EDITORIAL

A MATTER FOR CONCERN

IT IS A MATTER for concern that during the past fifteen years the increase in the medical population required to provide services to a growing Canadian population has been achieved only through the immigration of qualified physicians from other lands. It must further be a matter of concern to anaesthetists that a significant proportion of the candidates for training in the specialty during the same period have been immigrants. The danger in this situation lies, of course, in the fact that this source of trained physicians is limited—that it is, in fact, already exhausted. The physicians required to care for the anticipated growth of the Canadian population in the future must come from our own medical schools, and future trainees in the specialty of anaesthesia must be drawn from the graduates of our own schools.

During the past fifteen years too few of our own graduates have entered the specialty of anaesthesia. If this trend should continue, there will result a most serious shortage of qualified anaesthetists during the next decade. This will be the more serious because, with the growth of our smaller urban centres and the increasing supply of trained surgeons, a greater volume of surgery requiring the highest degree of anaesthetic skill and knowledge will be done in these areas. It is essential that more of the best graduates of Canadian medical schools should be attracted to the study of the specialty.

Our failure in the past to attract a larger number of bright young men to the study and practice of anaesthesia undoubtedly reflects the failure of teachers and practising anaesthetists to impress students and internes with the scope, challenge, and importance of anaesthesia. This requires not only imagination in presentation, but time and facilities. Imagination tends to wear thin in the teacher who must carry a full load of clinical work, who is chronically tired from loss of sleep, who has no time to think. To resolve this problem we require more teachers of anaesthesia in our universities, adequately compensated to permit them to make teaching a vocation rather than a spare time avocation; and further, we require adequate clinical investigation and laboratory facilities in these departments, not only to seek answers to the endless procession of problems in anaesthesia, but at the same time to demonstrate to the student and interne the interest and challenge of the specialty. Without these we will find ourselves unable to provide the anaesthetists which will be required by the Canada of 1970.

UN FAIT INQUIÉTANT

N'EST-CE-PAS UN FAIT INQUIÉTANT que, au cours des quinze dernières années, l'augmentation du nombre de médecins requis pour assurer les soins à notre population canadienne toujours croissante n'ait pu se réaliser que par l'immigration de médecins étrangers qualifiés. Pour les anesthésistes, ce fait doit être encore bien plus inquiétant car, au cours de cette même période, une bonne proportion des candidats à l'entraînement dans cette spécialité était des étrangers. La rançon de cette situation réside dans le fait que l'apport des médecins entraînés est limité et que, de fait, il est déjà épuisé. Les médecins dont on aura besoin pour traiter, à l'avenir, la population canadienne croissante devront sortir de nos écoles de médecine et les candidats futurs dans la spécialité d'anesthésie devront se recruter parmi les gradués de nos écoles.

De plus, au cours des quinze dernières années, un trop petit nombre de nos gradués se sont dirigés vers l'anesthésie. Si cette tendance persiste, il va en résulter, au cours de la prochaine décade, une diminution alarmante du nombre d'anesthésistes qualifiés. Et cela va devenir d'autant plus sérieux que le nombre de petits centres urbains augmente ainsi que le nombre de chirurgiens qualifiés et, dans ces endroits, une augmentation du volume de la chirurgie va exiger des anesthésistes hautement qualifiés, adroits et renseignés. Il devient donc essentiel qu'un plus grand nombre de nos brillants jeunes médecins se dirigent vers la spécialité de l'anesthésie.

Le fait que nous n'ayons pas réussi, dans le passé, à attirer vers la pratique de l'anesthésie un plus grand nombre de nos brillants jeunes médecins est un indice de l'échec, de la part des professeurs et de la part des anesthésistes pratiquant, auprès des étudiants et des internes, à promouvoir l'étendue, le défi et l'importance de l'anesthésie. Pour ce faire, il faut non seulement de l'imagination dans la présentation, mais aussi du temps et des facilités. Sans doute, l'imagination diminue chez le professeur qui doit accomplir du travail clinique à temps complet, qui, à l'état chronique, est fatigué par manque de sommeil et qui n'a même pas le temps de penser. Pour résoudre ce problème, nous exigeons, de la part de nos universités, un plus grand nombre de professeurs adéquatement rémunérés pour leur permettre de faire de l'enseignement: une vocation et non pas une occupation des temps libres; bien plus, dans ces départements, nous exigeons des facilités de laboratoire et d'investigation clinique adéquates non seulement pour trouver des réponses aux problèmes innombrables qui seposent en anesthésie, mais, aussi, pour pouvoir démontrer aux étudiants et aux internes l'intérêt de la spécialité et le défi qu'elle relève. Sans ces conditions, nous nous verrons dans l'impossibilité de produire les anesthésistes dont le Canada aura besoin en 1970.

THE CHANGING PATTERN OF NEUROMUSCULAR BLOCK*

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THE MUSCLE RELAXANTS have now been in general clinical use for just over fifteen years and it is therefore worthwhile to pause for a moment and take stock of the present position. If a popularity poll were to be conducted for the favourite relaxant drug in the world today, the winner would almost certainly be either d-tubocurarine or succinyldicholine.

At first glance, succinyldicholine appears to possess all the necessary attributes of the "perfect muscle relaxant," since it is extremely short-acting, it produces profound relaxation, and recovery from it is complete. A closer look at this drug, however, reveals certain disadvantages, and it is with these that this paper is principally concerned.

MUSCLE PAINS

It is now well known that following the use of succinyldicholine pains may arise the next day in many muscles throughout the body. These pains occur whether the succinyldicholine is given by single or repeated injection, and even when an infusion technique is used. On some occasions these pains are extremely severe and incapacitating. There is no doubt that their occurrence is clearly related to the amount of movement the patient undertakes in the first few hours after receiving the drug (see Table I).

TABLE I

INCIDENCE OF MUSCLE PAINS

Resting (in bed)	12 per cent
Ambulant	66 per cent

From time to time various claims have been made for methods used to reduce the incidence of these muscle pains. For example, it has been suggested that the bromide salt is free from an incidence of muscle pains, or, alternatively, that a small intramuscular dose of neostigmine given after the succinyldicholine paralysis prevents the onset of these distressing *sequelae*. Foster (1960) has made a study of some of these claims and his results are summarized in Table II.

It will be seen that the only satisfactory method of reducing the incidence of these pains in clinical practice is to give a small dose of a non-depolarizing drug before the injection of the succinyldicholine: the greater this dose, the less likely are muscle pains to occur, but at the same time there is a much greater

*Based on a paper read at the Second World Congress of Anaesthesiologists, Toronto, Canada, Sept., 1960.

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TABLE II

ATTEMPTS TO PREVENT MUSCLE PAINS

	Incidence
Succinyldicholine chloride v. bromide salt	no change
Neostigmine (1.0 mg. i.m. after S.C.)	no change
Gallamine (20 mg. before S.C.)	halved

risk of producing a prolonged response. Needless to say, such a practice of mixing relaxants cannot be recommended for routine clinical use.

EFFECT OF SUCCINYLDICHOLINE UPON THE HEART RATE

Another aspect of this drug that deserves brief mention is its effect upon the heart rate in man.

Martin of Heidelberg[8] first drew attention to the bradycardia, and even temporary cardiac arrest, that may follow the second and third injection of succinyldicholine, and Bullough[1] confirmed this finding.

Lupprian and Churchill-Davidson[7] have taken the matter one stage further and have attempted to analyse the changes and relate the incidence to the actual dose used. The main findings were as follows.

1. A slowing of the heart rate almost always occurs on subsequent doses of succinyldicholine.

2. In some cases, an actual arrhythmia may be observed and this may take almost any form.

3. Arrhythmias are related to the size of the dose administered and are very rarely seen when the dose is less than 50 mg. at a time.

4. These effects are probably due to vagal stimulation since they can be prevented by the previous intravenous injection of 1 mg. atropine.

INCIDENCE OF APNOEA DUE TO LOW PLASMA CHOLINESTERASE

The short action of succinyldicholine is owing to its being rapidly hydrolysed by the enzyme cholinesterase in the plasma. Occasionally a patient is encountered who either has a low titre of this enzyme or has inherited an abnormal form of this substance.

The incidence of this condition at our hospital over the past two years has been approximately one in every 2,000 cases to whom succinyldicholine has been administered. Although it is inconvenient when the apnoea is prolonged, such cases, if properly handled, should never give rise to alarm. The introduction of a new test paper from Austria has certainly simplified the measurement of plasma cholinesterase levels, and the anaesthetist can now use this method himself in the operating theatre to determine the enzyme level in a particular patient. Once a sample of plasma or serum has been obtained, it takes no more than twenty minutes to determine whether the patient has a normal value of plasma

cholinesterase. Very much more complex techniques are required to detect the extremely rare case of an abnormal type of enzyme.

In a study based upon this colour-paper (Churchill-Davidson and Griffiths)[8] it has been found that the new method corresponds closely with the values found by the alternative and somewhat complex technique of Michel.[9]

Dual Block

Our main investigations in the field of the muscle relaxants have centred upon the possible occurrence of a dual type of neuromuscular block; that is to say, whether—after repeated doses of a depolarizing drug—the nature of the block gradually changes from that of depolarization to that of non-depolarization.

This subject has great clinical significance because a non-depolarizing block can be reversed by an anticholinesterase drug, whereas a depolarizing block is only made worse.

The results can best be illustrated by actual examples of the effect of the various relaxant drugs on neuromuscular transmission. In the cases that follow, the ulnar nerve is stimulated electrically and the resultant contraction of the hand muscles is recorded electromyographically.

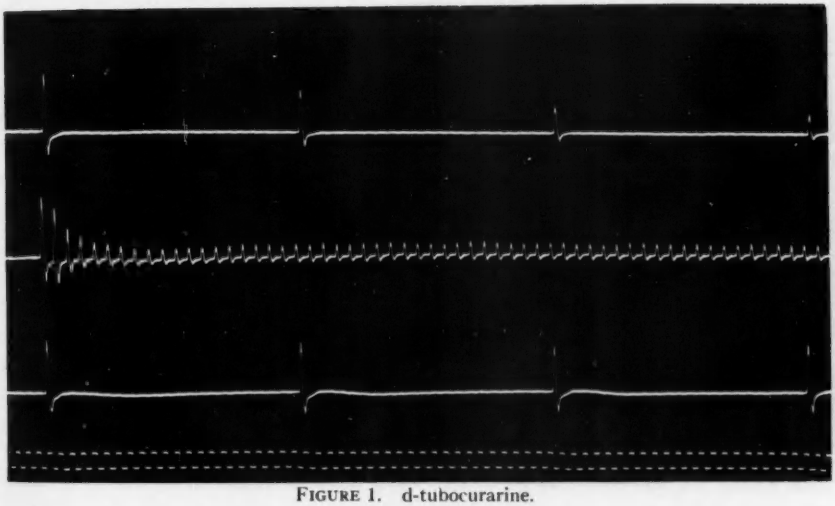

Figure 1. d-tubocurarine.

In Figure 1 note the characteristic way in which successive responses "fade" with both slow and fast rates of stimulation. Observe also the way in which neuromuscular transmission is briefly improved by a burst of fast or tetanic stimulation—the so-called post-tetanic facilitation.

These changes are diagnostic of a non-depolarizing block such as d-tubocurarine produces.

In direct contrast with the previous figure, Figure 2 indicates the way in which both slow and fast rates of stimulation are well maintained and the com-

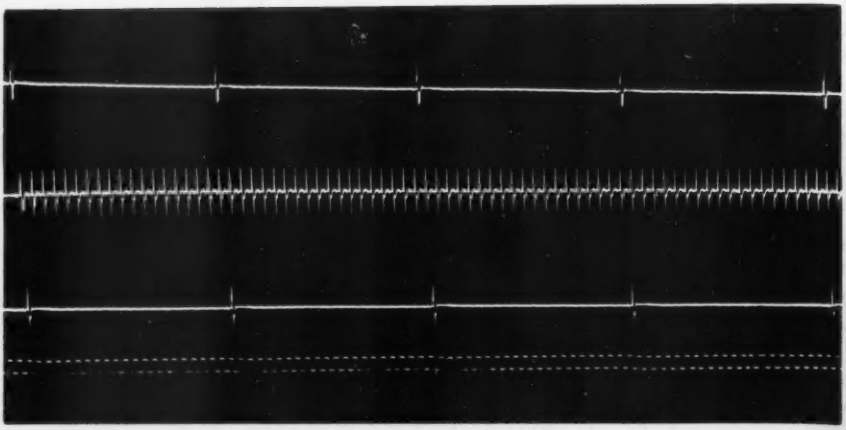

FIGURE 2. Effect after small dose of depolarizing drug, for example, succinyldicholine.

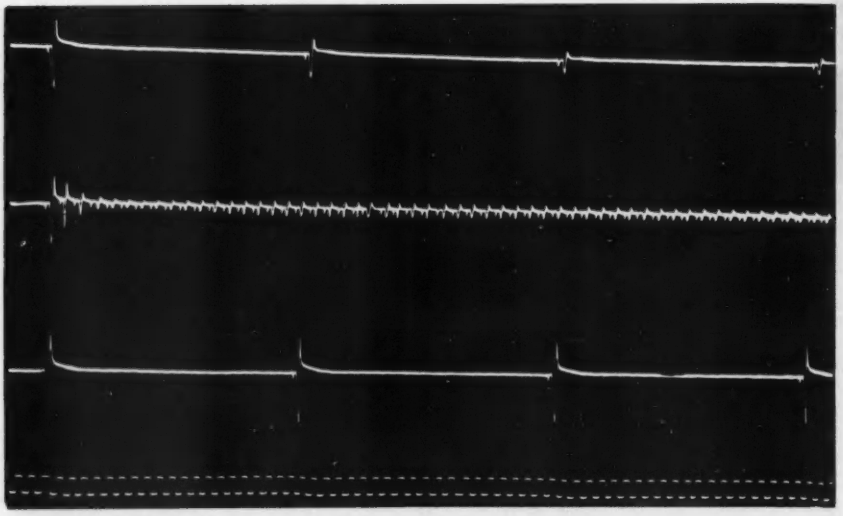

FIGURE 3. Effect of large dose of a depolarizing drug.

plete absence of post-tetanic facilitation. Exactly the same changes are seen after a small dose of decamethonium and for research purposes these changes are easier to study with this drug because it is not destroyed, as is succinyldicholine, by plasma cholinesterase.

Figure 3 illustrates the effect of a large total dose of a depolarizing drug, that is, in all 18 mg. decamethonium. Observe how repeated doses of the depolarizing drug have led to a gradual change in the pattern of the neuromuscular block until it finally closely resembles that seen after d-tubocurarine.

The effect of neostigmine upon the final pattern in Figure 3 is equally dramatic (Fig. 4), showing that a dual block had been produced which was reversed by neostigmine.

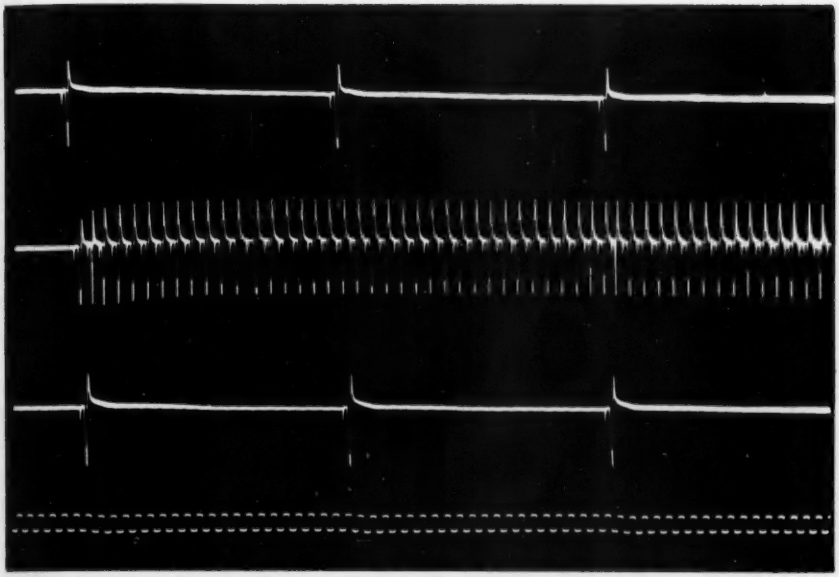

FIGURE 4. Effect of neostigmine upon the final pattern of Figure 3.

Some twenty patients were studied using both decamethonium and succinyldicholine.[2] The first signs of a dual block could be recognized in this series after 500–1500 mg. succinyldicholine and after 6–20 mg. decamethonium. These results imply that if one continues giving a depolarizing drug by infusion or intermittent injection the point will be always reached in every patient when a full dual type of neuromuscular block is present. In one most unusual case outside this series, the signs of dual block have been observed after a single dose of only 100 mg. succinyldicholine.

It must be emphasized, however, that in this study a deliberate attempt was made to produce the signs of a full dual block. Occasionally, to our bitter disappointment, the surgeon finished the operation before this goal could be achieved! From the clinical aspect such cases can present a real problem, since, without the help of diagnostic instruments, the anaesthetist cannot tell whether the neuromuscular block at the end of operation is predominantly a depolarizing or a non-depolarizing one.

A dual block should always be suspected after an infusion of succinyldicholine if the patient recovers his muscle tone only slowly and also has a persistently poor volume of ventilation. The use of the accessory muscles of respiration and "tracheal tug" are also suggestive signs.

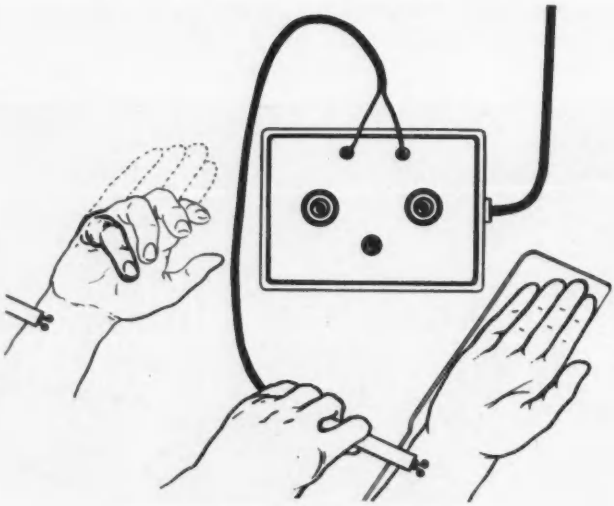

FIGURE 5. Peripheral nerve-stimulator.

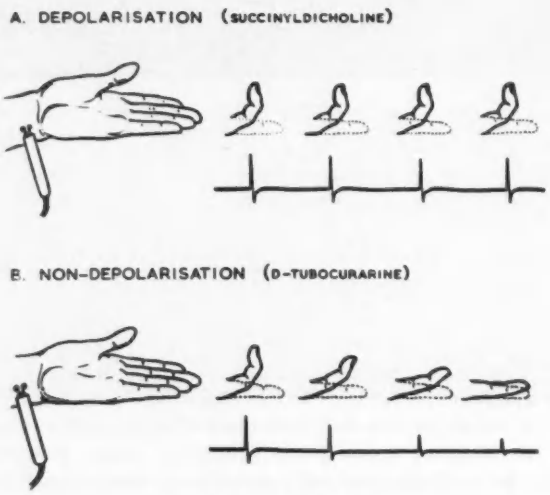

FIGURE 6

Identification of the exact type of block that is present in the peripheral muscles can be made at any time with a peripheral nerve-stimulator (Fig. 5).

If the ulnar nerve at the wrist is stimulated electrically, the mechanical movement of the fingers will reveal which type of block is present in exactly the same way as will the electromyographic responses (Fig. 6).

If the fingers move rhythmically and the contraction is sustained, a depolarization block is present. On the other hand, if the response rapidly fades away and post-tetanic facilitation is present, the block is of the non-depolarizing type and will be improved by an injection of neostigmine.

A simple peripheral nerve-stimulator is an essential piece of apparatus for any anaesthetic department. It is not needed very often, but it can at any time tell the anaesthetist firstly whether a neuromuscular block is actually present and, secondly, what type of block prevails.

Conclusion

These studies on the disadvantages of succinyldicholine are not intended to detract from what is a most useful clinical relaxant. Nevertheless, they indicate the urgent necessity to find a short-acting non-depolarizing drug. At the meeting in Venice on muscle relaxants in 1958, just such a compound (namely "Compound 41") was described, which appeared from animal experiments to be highly promising.[4] Alas! the investigations in man showed that it produced profound histamine release with severe hypotension and tachycardia, and was quite unsuitable for clinical use. Haining[5,6] has stimulated our interest in a series of tropine derivatives. By a careful pharmacological analysis he has produced several most interesting compounds. Some have had a shorter action than succinyldicholine, while others have proved much longer-acting. All have been found to act like d-tubocurarine.

One compound, "DF 752" is of particular interest (Fig. 7).

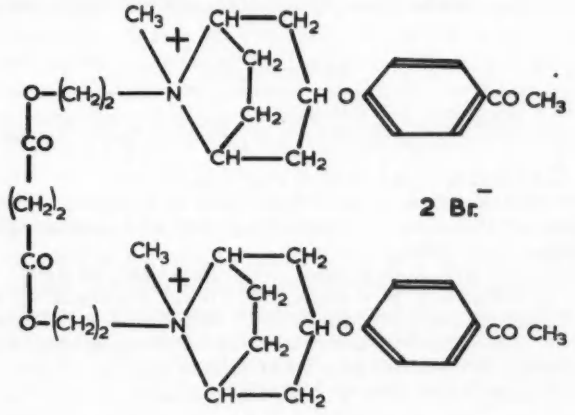

Figure 7

Unfortunately, this is not the very short-acting drug we were seeking. Nevertheless, in a limited clinical trial it has shown certain advantages over gallamine triethiodide. It has a shorter duration of action (10–15 min.) and the degree of tachycardia is lower. Paralysis of the laryngeal muscles is rapidly achieved.

The ideal short-acting non-depolarizing drug with minimal side-effects, that will replace succinyldicholine, still eludes us; but the search goes on.

Acknowledgments

Figures 1, 2, 3, and 4 previously appeared in *Anesthesiology* and Figures 5 and 6 in the *British Journal of Anaesthesia*. I should like to thank the editors of these journals for kindly permitting me to reproduce them here.

Résumé

Il existe une gamme étendue de relaxants musculaires à action dépolarisante utilisables en clinique, mais le succinyldicholine est le seul qui jouisse d'une popularité qui ne s'est jamais démentie. Toutefois cette substance présente deux inconvénients principaux. D'une part, elle entraîne des douleurs musculaires au cours de la période post-opératoire; diverses tentatives pour réduire la fréquence de cette complication sont discutées. D'autre part, toutes les substances à action dépolarisante sont susceptibles de modifier progressivement le blocage sousjacent jusqu'à ce qu'apparaisse un blocage du type non dépolarisant. En bref, on se trouve en présence d'un double blocage. L'auteur expose l'incidence et les conditions nécessaires à l'apparition de ce dernier type de blocage (blocage double).

Aussi, le désir de surmonter les principaux inconvénients du succinyldicholine a-t-il conduit à rechercher intensivement un type de relaxant musculaire à action brève et non dépolarisante. Les résultats de ces recherches sont exposés.

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EXPERIMENTAL AND CLINICAL EXPERIENCE WITH TOXIFERINE (ALKALOID OF CALABASH CURARE)*

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THE PRESENT MUSCLE RELAXANT DRUGS do not yet fulfil all the desires of the anaesthetist with regard to variation of the duration of action, the possibility of being antagonized, and the avoidance of side-effects. The search for further relaxant drugs is therefore justified.

In 1958, Karrer and Schmid (Zürich) isolated the chief alkaloids from Calabash curare and determined their chemical structure. Waser investigated their pharmacological properties and subsequently, together with the anaesthetist Harbeck (Zürich), defined the possibilities of their clinical use.

In order to form our own opinion, we used Toxiferine, the drug which is perhaps the most appropriate for clinical use, in 30 trials on conscious volunteers and 100 patients during anaesthesia, in the Department of Anaesthesia of the University Clinics, Mainz.

METHODS

Auto Trials

(*a*) *Volunteers.* The three volunteers were assistants in the Department of Anaesthesia who were familiar with the action of muscle relaxants because, in the anaesthesiological practice, they had worked daily with such drugs for years. Thus we could rely on the co-operation of the volunteers and were able to sufficiently exclude any subjective influence on the results by the volunteers. In order to determine the relationship between effect and body weight, we chose volunteers (of about the same age) who differed markedly in body weight (44, 63, and 82 kg.).

(*b*) *Technique of injection.* The Toxiferine solution was administered intravenously. The injection time varied between 5 and 90 sec. We chose the extremely rapid injection of five seconds in order to achieve a high initial blood level enabling us, at the same time, to obtain a better understanding of possible side effects. The slower injection was studied because this lies nearer the mode of administration under clinical conditions or represents the pharmacologically appropriate mode of administration. In varying the speed of injection of the same dose, we were able to demonstrate variations in the intensity and duration of action with Toxiferine, as expected from experience with other curare preparations.

(*c*) *Form and technique of recording.* Blood pressure, pulse rate, vital capacity, respiratory rate, and grip strength were recorded at intervals of one to two

*Paper read at the World Congress of Anaesthesiologists in Toronto, Sept. 8, 1960.

†Department of Anaesthesia of the University Clinics, Mainz (Director: Professor R. Frey, M.D., F.F.A.R.C.S.).

minutes. In addition, we registered the latent period, the duration of head drop and of paralysis of deglutition which is so important in clinical application. The grip strength was measured with the ergometer, the vital capacity with the volumeter of the anaesthetic apparatus (Draeger). We purposely renounced further spirographic measurements, firstly because additional recordings would have been impossible without prolonging the test periods and secondly because we did not want to overtire the volunteers; both would have impaired the accuracy of the results.

Clinical Application

(*a*) *Clinical material.* The only criteria for the selection of patients for the clinical use of Toxiferine was the duration of the intended operative intervention, that is, whether an operation of more than one to two hours' duration was anticipated. Age, general condition, or concomitant diseases (if these permitted curarization at all) were not taken into consideration. Our clinical material, therefore, consisted mainly of middle-aged to elderly adults. The drug was rarely administered to children, chiefly because such prolonged operations are less frequent in children. Toxiferine has not been given to infants or small children.

(*b*) *Operations.* The drug was used in long operations, mainly abdominal and thoracic surgery, such as partial gastrectomy (including bleeding and perforated ulcers), total gastrectomy, splenectomy, hemicolectomy, amputation of the rectum, cholecystectomy with choledochotomy for which a rather long operation was to be anticipated, resection of the pancreas, pneumonectomy, lobectomy, and resection of the esophagus and cardia. In addition, Toxiferine was used in the resection of advanced goitre and, less frequently, in protracted orthopaedic interventions, such as pseudoarthrosis, open reduction of old fractures, and so on, whenever strong curarization seemed appropriate; not every surgeon wishes it.

In urological operations we were more reserved: although we used Toxiferine without hesitation in operations for ureteral or renal calculi, or plastic surgery of the renal pelvis in patients in whom the appropriate investigations indicated intact renal function, we preferred not to use Toxiferine in patients in whom this could not be assumed. It is known from animal experiments that Toxiferine —as other synthetic non-depolarizing relaxants—is not reduced, but excreted quantitatively through the kidneys almost unchanged.

(*c*) *Technique of Anaesthesia.* Our anaesthetic procedure was as follows: after premedication with meperidine and atropine, anaesthesia was induced intravenously with thiopental. Intubation was then performed under succinylcholine apnoea. Anaesthesia was maintained with a N_2O-O_2 mixture with or without the addition of small amounts of halothane. After the return of spontaneous respiration, Toxiferine was administered intravenously in a dose which produced complete paralysis of the spontaneous respiration or at least to such a degree that respiration could be controlled without resistance. In children, instead of intubation under succinylcholine apnoea, this was performed during spontaneous respiration under halothane drip anaesthesia. Intubation under Toxiferine relaxation would, of course, also be possible. We did not, however, see any

reason to change the mode of intubation which is usual in our clinic also for didactic reasons.

If there was sufficient spontaneous respiration at the end of the operation (measured with a flow-meter and compared with the values found before curarization), the patient was extubated. If there were no signs of residual curarization, that is, if the patient was able to open his eyes completely and, above all, to swallow, decurarization was not necessary and therefore omitted. If there was some residual curarization, we first administered atropine intravenously, then physostigmine* intravenously, and—according to the degree of the remaining curarization—perhaps pyridostigmine† (generally 1 mg. intramuscularly and 1 mg. intravenously). If no signs of spontaneous respiration were detectable at all, at the end of the operation (this occasionally occurs in operations which, contrary to expectation, end as exploratory laparotomies) artificial respiration was continued at any rate until a measurable, though low, spontaneous respiration could be detected and then only decurarization was performed.

Experimental Results

Histamine Effects

(*a*) ***On the skin.*** Intravenous injection did not cause cutaneous side-effects in any of the volunteers; no exanthematous reactions which could have been the result of a histamine release were observed.

In order to define possible histamine effects more exactly, we compared Toxiferine with other natural and synthetic non-depolarizing relaxants in the intracutaneous test. We injected dilutions of Toxiferine and of d-tubocurarine, methylcurarine, gallamine, physiological saline, and histamine. The individual relaxants were diluted according to their clinical effectiveness, on the assumption that Toxiferine is 10 times, methylcurarine 3 times, and gallamine 0.25 times as effective as d-tubocurarine. We investigated the substances in two different series of dilutions; one contained 30 γ Toxiferine per injection, the other 3 γ Toxiferine, and the corresponding amounts of the other relaxants. The reactions were fully developed after 10 to 15 minutes and wore off in the course of the next hour or two. The injection of physiological saline caused only a slight unspecific reddening. All the relaxants caused more marked reddening and wheal, the intensity being greatest with d-tubocurarine, medium with methylcurarine, and least with Toxiferine and gallamine. The two latter substances produced about equally strong reactions. The duration of the reactions corresponded to their intensity: the wheals and reddenings of the Toxiferine and gallamine injections wore off first, then those of methylcurarine, and lastly those of d-tubocurarine. Among the series of weaker dilutions, a slight reddening at the site of injection of d-tubocurarine could be observed after four hours. It, therefore, outlasted the effect of the injection of pure histamine.

(*b*) ***On salivary secretion.*** In our auto-investigations, at least those with small doses, intravenous injection of Toxiferine caused no increase in salivation, which

*Prostigmin.
†Mestinon.

was marked only after d-tubocurarine. We cannot judge the effect on salivary secretion of higher doses (23 γ/kg. body-weight) because atropine was given as premedication in order to eliminate secretion as far as possible. These doses caused complete deglutition paralysis of 15 to 20 minutes duration, so that even normal salivary secretion would have increased the danger of aspiration.

Effect on Blood Coagulation

Knowing that d-tubocurarine prolongs the prothrombin and coagulation time—a property which is generally considered to be due to heparin release—and because with clinical use of Toxiferine we had occasionally observed an unusual degree of parenchymatous haemorrhage during the operation, we also carried out prothrombin estimations (using the two-phase method) in some of our

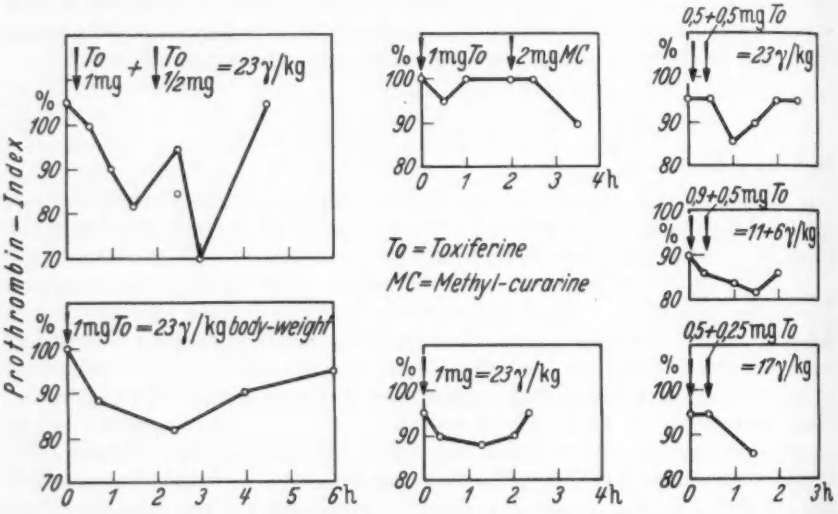

FIGURE 1. Changes in coagulation time in the hours following injection of Toxiferine: regular prolongation of coagulation time.

volunteers. The results varied considerably from test to test. Nevertheless, there was a regular fall in prothrombin which in some of the cases, however, especially at low doses, was only 5 to 10 per cent and, therefore, had no significance. At higher doses, the reductions were generally more marked (from 10 to 20 per cent). In subsequent tests at the same dose (1 mg. = 23 γ/kg. body-weight) however, the prothrombin reduction varied from 5 to 23 per cent in one individual subject and a definite relationship could not, therefore, be determined. At a further increased dose of 1.5 mg. (fractionate injection of 1 and 0.5 mg.), there was a reduction of 35 per cent. A corresponding slight prolongation of the coagulation time was occasionally observed. In contrast to d-tubocurarine with which the maximum effect on blood coagulation occurs a few minutes after the injection, we observed the maximum effect of Toxiferine only after one to two hours.

Our clinical observations also agree with this: with laparotomy we hardly ever saw increased haemorrhage when severing the subcutaneous tissue and the muscular layers, unless an increase in blood pressure had occurred because the plane of anaesthesia was too light at the beginning of the operation; whereas we repeatedly observed increased haemorrhage from the mucosa in suturing anastmoses, for example, with gastrectomies, although the circulation was constant and the blood pressure kept low.

We should like to emphasize that such an increased haemorrhagic tendency has been observed only in a small number of cases. One must take this difficulty into account, however, and, in cases in which increased haemorrhage hinders the preparation or evokes additional dangers (for example, brain tumors, liver injuries, and so on), be more reluctant to give large doses of relaxants.

In operations of long duration in which Toxiferine is indicated as relaxant, the maximum of the coagulation disturbance occurs during the course of the operation. In our opinion, there is no danger of increased secondary haemorrhage. None was observed in the cases we have treated to date.

Pulse Rate

Changes in the pulse rate immediately after the injection of Toxiferine, and attributable to the relaxant, have not been observed in our investigations. At the peak of curarization, with marked restriction of spontaneous respiration or during artificial respiration, there were, of course, especially in the first trials, occasional slight increases in the pulse rate (not exceeding 100/min.) which were of a psychogenic origin and humanly understandable. In one volunteer who underwent a total of 15 such tests, the initial pulse rate remained unchanged for the whole duration of some of the later tests.

Blood Pressure

The same applies to the blood pressure values which were measured at intervals of one-half to two minutes. A significant fall in blood pressure following Toxiferine administration was never observed (in contrast, there was a fall in blood pressure of 20 mm. systolic at times following even small doses of d-Tubocurarine Chloride and dimethyl-d-tubocurarine). Occasionally, also at the peak of the curarization, there was a slight increase in blood pressure (again due to psychogenic reasons and sometimes perhaps to a rise in the CO_2 tension) with subsequent decrease to the norm or somewhat below as the curare effect wore off.

Dose

The mode of action of Toxiferine is the classical curarelike one, that is, nondepolarizing. The course of the paralysis, therefore, proceeds in the same manner and order as that due to d-tubocurarine. Toxiferine, however, is about 15 times more effective in the human than d-Tubocurarine Chloride, as shown by comparative studies of the two substances.

(*a*) *Effect on the ocular muscles.* The influence on the ocular muscles is the first to be felt and also lasts the longest. The sensitivity of the individual ocular muscles also varies (one can observe this best as the curare effect wears off, since

this takes place particularly slowly in the ocular muscles). From investigations with other non-depolarizing relaxants, it is known that the Mm. recti interni are especially sensitive to curare. The same has been observed with regard to Toxiferine: as the last objective symptom before the effect wore off, there remained a divergent strabismus even when the patient was able to stand upright again. Only a very small amount of Toxiferine is apparently necessary to produce this paralysis: after intravenous injection of only 0.25 mg. Toxiferine (corresponding to 5.6 γ/kg. body-weight) we were able to observe this effect, subjectively experienced as diplopia, without paralysis of the M. levator palpebrae. This was the smallest intravenous dose given in our tests and we are inclined to assume that even smaller doses would produce this paralysis. (This assumption is based on an observation made accidentally and involuntarily in one of our histamine tests. We intended to inject 30 γ Toxiferine intracutaneously and, due to incorrect technique, we apparently hit a small subcutaneous vessel. Within a few minutes the volunteer suffered from diplopia and strabismus. One has, however, to take into consideration that the same volunteer had received other relaxants in corresponding intracutaneous dosage, so that this incipient curarization might be attributed to a summation effect. Therefore, 30 γ cannot be considered as a dose causing initial paralysis of the ocular muscles.)

(*b*) "*Head drop*" *dose.* The "head drop" dose which is so important in the animal experiment is of no interest in the human. In our investigations, "head drop" occurred at the reduction of the grip strength to 15–30 per cent of the norm. In other words, the "head drop" dose approximately corresponds to that which reduces the grip strength to 15–30 per cent of the norm.

(*c*) *Influence on vital capacity and grip strength.* With sufficiently high doses, the total skeletal musculature, including the peripheral musculature of the respiratory tract and the diaphragm, are paralysed during the further course of the curarization. In our tests, the effect on the respiration, measured by the vital capacity, and the reduction of the grip strength followed a parallel course, in that both decreased in a linear manner to the minimum which was reached within five minutes, on the average. In figures, however, the reduction of the vital capacity was markedly less than that of the grip strength. A dose (17 γ/kg. body-weight) which reduced the grip strength to about 40 per cent of the norm, reduced the vital capacity only to about 70 per cent of the initial value. An increased dose (23 γ/kg. body-weight), which lowered the grip strength to 0 per cent, still left a vital capacity of 30 per cent. This difference must be attributed to a reduced sensitivity of the diaphragm because the remaining peripheral musculature of the respiratory tract as well as the skeletal muscles were paralysed. Where a sufficient spontaneous respiration and a relatively high vital capacity remained, there was pure diaphragmatic respiration.

With respect to the relationship between the reduction of the grip strength and the reduction of the vital capacity, Toxiferine corresponds to d-tubocurarine, whereas the effect of methylcurarine* on the vital capacity was even lower: the dose of 0.1 mg./kg. body-weight, for instance, reduced the grip strength to 0 per cent; the vital capacity, however, only to 60 per cent (in agreement with Sadove's results).

*Dimethyl-d-tubocurarine chloride.

Whereas, at the onset of action, the vital capacity and the grip strength uniformly decrease, with the wearing off of the effect, the vital capacity is normalized more rapidly than the grip strength. After injection of 1 mg. = 23 γ/kg. Toxiferine, for instance, the grip strength was still less than 5 per cent at the time when the vital capacity had again reached 50 per cent. At the time when the vital capacity was at 80 per cent, the grip strength was only 20 per cent; in other words, 50 per cent of the vital capacity was reached after 17 minutes, 50 per cent of the grip strength only after 38 minutes. The effect of this substance on the grip strength therefore lasted twice as long as that on the vital capacity. The relatively prolonged influence on the grip strength is even more marked when Toxiferine is injected more slowly; especially in this respect there were marked differences in the effect in relationship to the speed of injection (see Figs. 2 and 3). With rapid injection, normalization of the grip strength and vital capacity is achieved more slowly than with slow injection. With rapid injection, however, the prolongation of the action on the grip strength was more marked than that on the vital capacity.

Duration of Action

More than with other shorter-acting relaxants, the duration of action of Toxiferine depended on the dose administered. In addition, as mentioned before, it depends to some extent on the speed of the injection.

When increasing intravenous doses of Toxiferine (0.25 mg., 0.5 mg., 0.75 mg., 1 mg.) were administered to a volunteer weighing 44 kg., restriction of the vital capacity below 70 per cent of the norm and of the grip strength below 40 per cent of the norm was found to be present for the following periods:

Dose	Duration of action	
	Vital capacity below 70 per cent of the norm	Grip strength below 40 per cent of the norm
0.25 mg. = 5.6 γ/kg.	—	—
0.5 mg. = 11 γ/kg.	7 min.	8min.
0.75 mg. = 17 γ/kg.	12 min.	18 min.
1.0 mg. = 23 γ/kg.	26 min.	37 min.

Vital capacity and grip strength had returned to normal after the following lengths of time: 0.25 mg. = 5.6 γ/kg. in 9 min. and 12 min.; 0.5 mg. = 11 γ/kg. in 15 min. and about 20 min.; 0.75 mg. = 17 γ/kg. in 20 min. and about 50 min.; 1.0 mg. = 23 γ/kg. in 60 min. and about 60 min.

The duration of "head drop" after 23 γ/kg. was 16–17 min. depending on the rapidity of injection; the duration of deglutition paralysis was 15–20 min. after the same dose. A marked effect on the ocular muscles was observable for two hours. After this period, the volunteers were generally able to stand up and to walk—though somewhat unsteadily—on the level floor. Minor after-effects such as unsteadiness in climbing stairs, incapacity to read for long because of slight

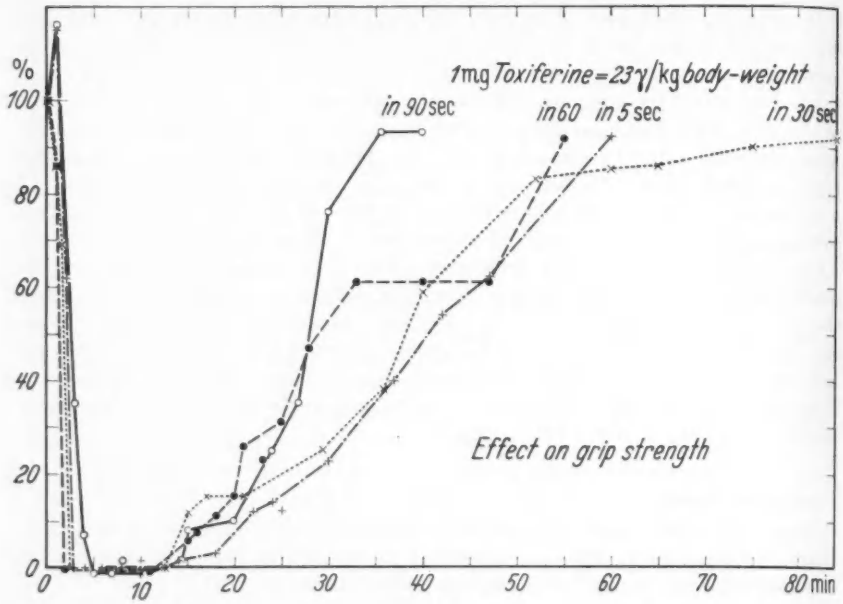

FIGURE 2. Effect of 1 mg. Toxiferine on grip-strength (summary of the results of 4 trials).

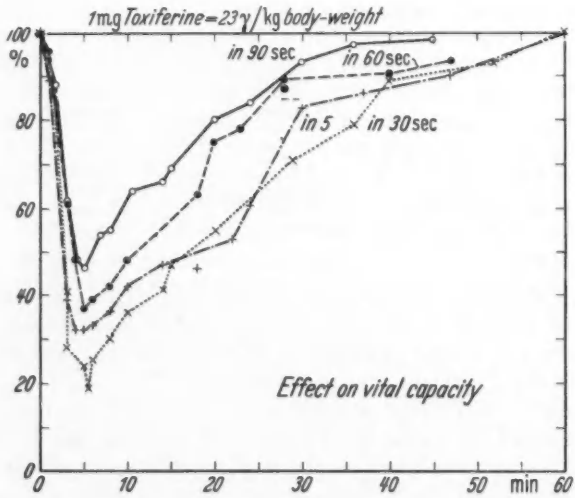

FIGURE 3. Effect of 1 mg. Toxiferine on the vital capacity (summary of the results of 4 trials).

weakness in the ocular muscles, increased fatigability following repeated rapid movements could be observed even five hours after the injection.

In obese persons, the same dose per kg. body-weight produced more marked effects of somewhat longer duration. This is in agreement with the fact known from experience with other curare preparations that the dose of a relaxant has to be reduced in the obese as well as for persons who are considerably underweight.

Accumulation

(*a*) *With repeated Toxiferine administration.* One of the most impressive properties of Toxiferine is its marked property of accumulation following repeated injections. Although this was to be expected because of the long duration of action of this substance and the slow excretion, known from animal experiments, we were repeatedly surprised at the extent of this accumulation.

In the first instance, we assessed these properties by subsequent injections of small doses of Toxiferine at short intervals of 15–20 min. compared with equivalent doses of d-tubocurarine and methylcurarine (see Figs. 4 and 5). A very

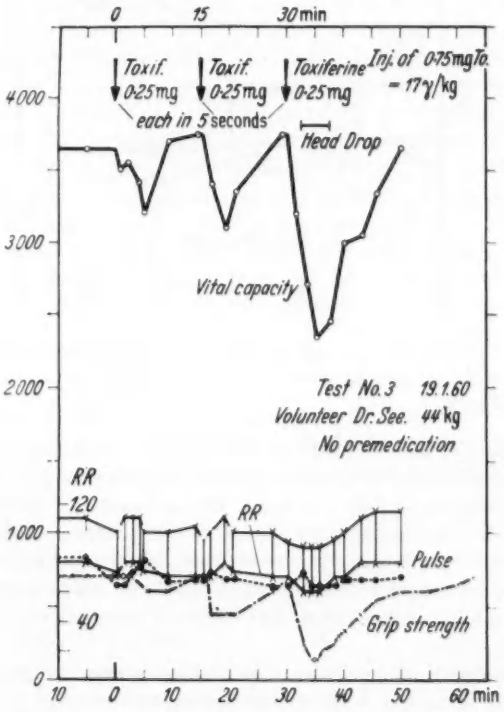

FIGURE 4. Cumulative effect of repeated intravenous injections of 0.25 mg. Toxiferine.

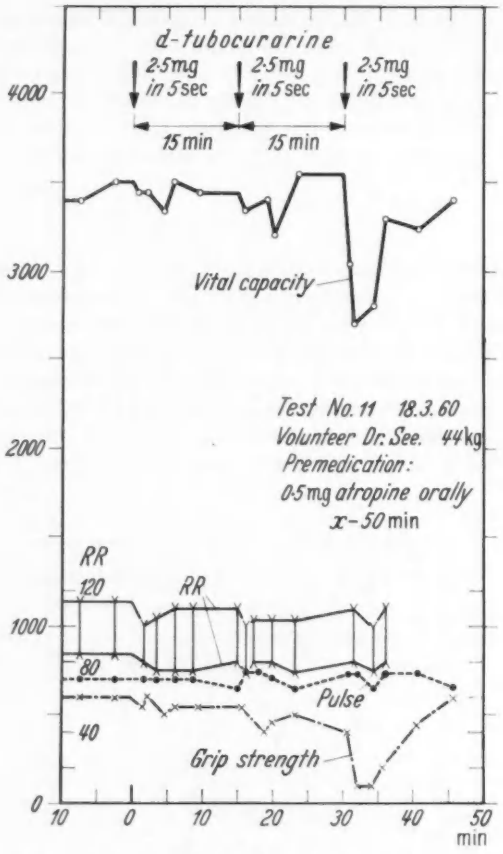

FIGURE 5. Cumulative effect of repeated injections of 2.5 mg. d-tubocurarine in the same volunteer as in Figure 4.

marked accumulation with regard to vital capacity and grip strength resulted from the administration of Toxiferine. Repeated doses of d-tubocurarine likewise produced these effects though they were less pronounced. Methylcurarine produced almost no accumulation with regard to vital capacity, which corresponds to its generally minor effect on the respiration, whereas a certain accumulation with regard to grip strength was observed. The differences between the individual relaxants were not as marked when the intervals between the individual injections were short.

(*b*) ***Combination with other relaxants.*** For this purpose, we changed the experimental conditions in such a manner that we allowed two hours to pass after the initial injection of 1 mg. = 23 γ/kg. until, apart from the above mentioned slight after-effects such as easy fatigability of the musculature, no subjective

curare effects were felt (objectively, these had worn off earlier). We subsequently injected ½ mg. Toxiferine (that is, half the initial dose) in a first test, 2 mg. methylcurarine in a control test (that is, the dose which, as single dose in the same volunteer, had decreased the vital capacity to 90 per cent of the norm and the grip strength to 60 per cent), and 22 mg. succinylcholine in a third test (the full relaxant dose calculated for this subject).

The results are shown in the Figures 6, 7, and 8. A second injection of ½ mg. Toxiferine two hours after the injection of 1 mg. Toxiferine produced an equally strong and even longer lasting effect on the vital capacity and grip strength than the injection of 1 mg. Toxiferine given two hours earlier. Although the single dose of dimethyl-d-tubocurarine hardly made any impression on the volunteer, the effects of this second injection on the respiration were not the minor ones otherwise typical of methylcurarine: on the contrary, the respiratory impairment was in this case so strong that artificial respiration had to be performed for ten minutes. This had not been necessary with the injection of Toxiferine alone. The results prove that two hours after the injection of Toxiferine, a great part of this relaxant, at least half of the dose administered, must still be present and active. In contrast to this, the subsequent injection of succinylcholine two hours after Toxiferine administration had a normal effect: no cumulative effect was to be anticipated because this is a relaxant of the depolarizing type. However, there was no reduction of the effect. The muscle pains which appeared after the injection were also the same as those occurring after a single injection of succinylcholine.

(*c*) ***Combination with anaesthetics.*** The intensity and duration of the effect of the individual Toxiferine doses mentioned above apply to injections in conscious volunteers who—apart from small amounts of atropine administered with the highest doses of Toxiferine—had received no pretreatment. In any case, there is an additive effect on the muscle relaxation produced by Toxiferine during anaesthesia, and with some anaesthetics (for example, ether and halothane), a potentiating effect, with regard to both the intensity and above all the duration of the effect.

Side-Effects

No side-effects whatsoever have been observed in any of our tests with Toxiferine, neither irritation of the wall of the vein associated with pain at the site of injection nor any general complaints. A certain feeling of giddiness which occasionally appeared at the beginning of the paralysis also occurs with paralysis of the ocular muscle due to other causes, and disappeared when the volunteer closed his eyes. We have never observed exanthematous skin reactions, increased salivation, or changes in blood pressure or pulse rate.

Possibility of Being Antagonized

Toxiferine, as other non-depolarizing relaxants, can be antagonized by cholinesterase inhibitors. In our tests, we did not make use of this possibility as we were anxious to observe the wearing off of the effect. We shall revert to this problem when discussing the clinical use of Toxiferine.

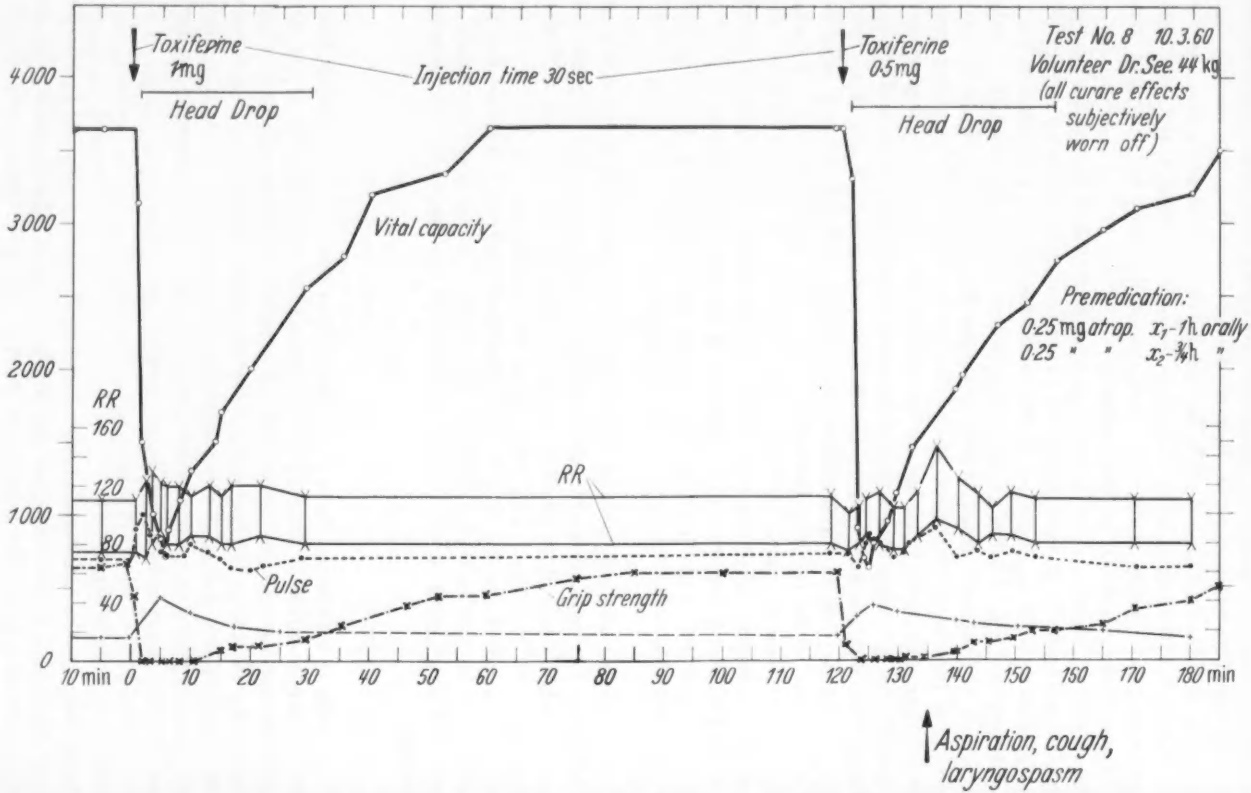

FIGURE 6. Cumulative effect of 0.5 mg. Toxiferine given two hours after 1 mg. Toxiferine in the same volunteer.

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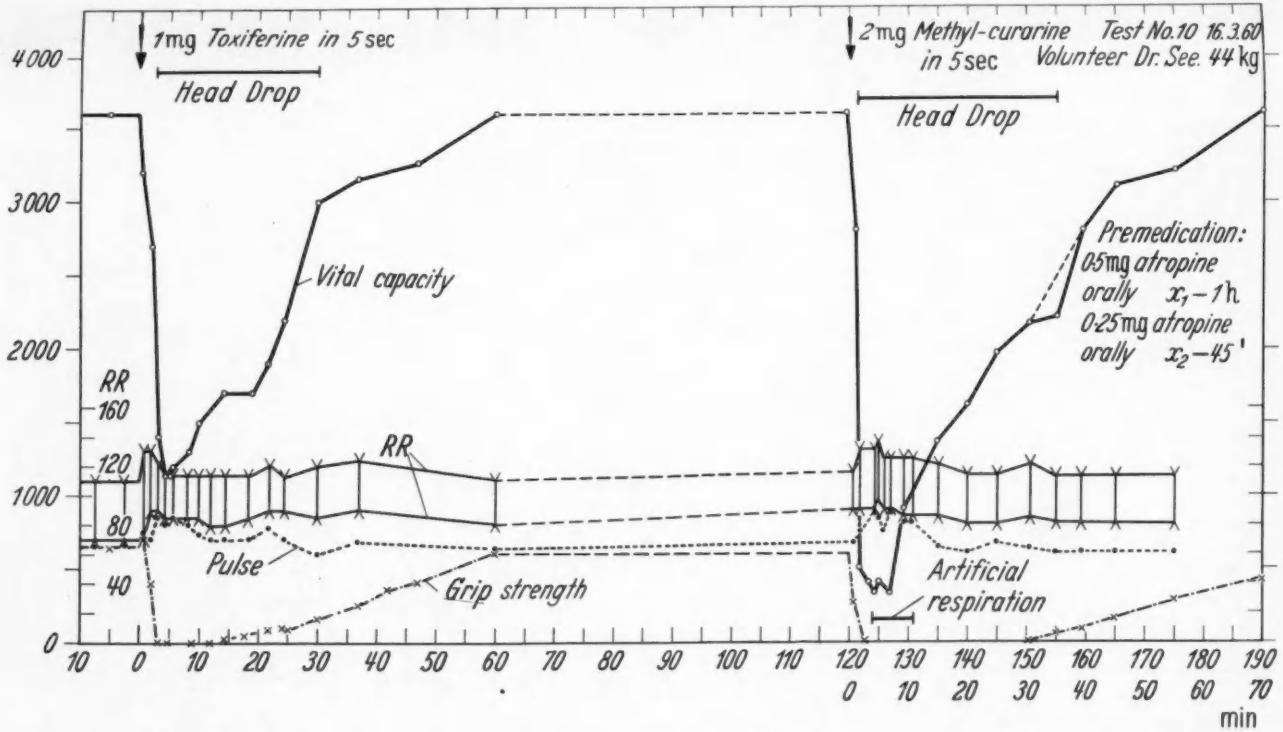

FIGURE 7. Cumulative effect of 2 mg. dimethyl-d-tubocurarine given two hours after 1 mg. Toxiferine in the same volunteer.

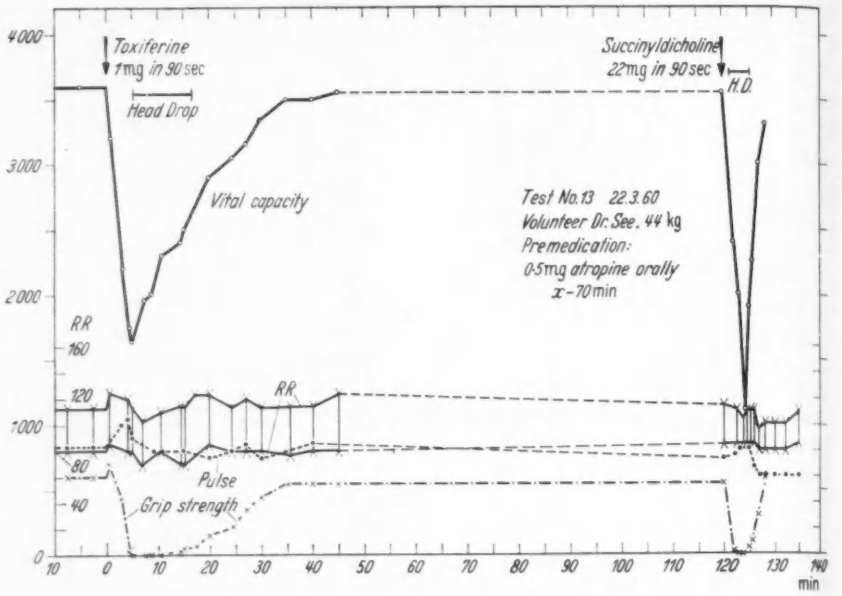

FIGURE 8. Absence of cumulative effect of 22 mg. succinylcholine given two hours after 1 mg. Toxiferine in the same volunteer.

CLINICAL RESULTS

Histamine Effects

As in the tests, we did not observe histamine effects with the clinical use of Toxiferine. Laryngospasm, bronchospasm, or other manifestations which might be attributed to histamine release never occurred, although we intentionally excluded antihistaminics from the pretreatment of cases chosen for Toxiferine administration.

Pulse Rate and Blood Pressure

With regard to the effects on circulation, Toxiferine administration under anaesthesia also confirms the results obtained in volunteers. There were no effects on circulation which could have been attributed to Toxiferine. In the majority of cases, anaesthesia was maintained with halothane. In these, there was occasionally a fall in blood pressure and pulse rate following complete relaxation and some minutes after respiration was controlled, especially if this was performed as a single phase direct pressure respiration. This effect is the result of the rapid flow of halothane and not of the muscle relaxant. Such an effect was never observed when subsequent doses of Toxiferine were injected during the course of the operation. Even more clearly than these observations, the results of our auto-investigations confirm that Toxiferine has no such effect on the circulation.

Clinical Dosage

In order to achieve strong relaxation for protracted operations, we generally injected 2 mg. Toxiferine at the beginning of the operation. In cachectic or considerably underweight patients, we reduced the dose to 1–1.5 mg. In almost all the cases, complete paralysis of spontaneous respiration was achieved within one and a half to two minutes with these doses, or at least such a restriction of the respiration that it could easily be controlled. If, in very muscular men, respiratory paralysis was not achieved with 2 mg., a maximum of a further ½ to 1 mg. was immediately injected. Only in occasional cases were 3 mg. required,

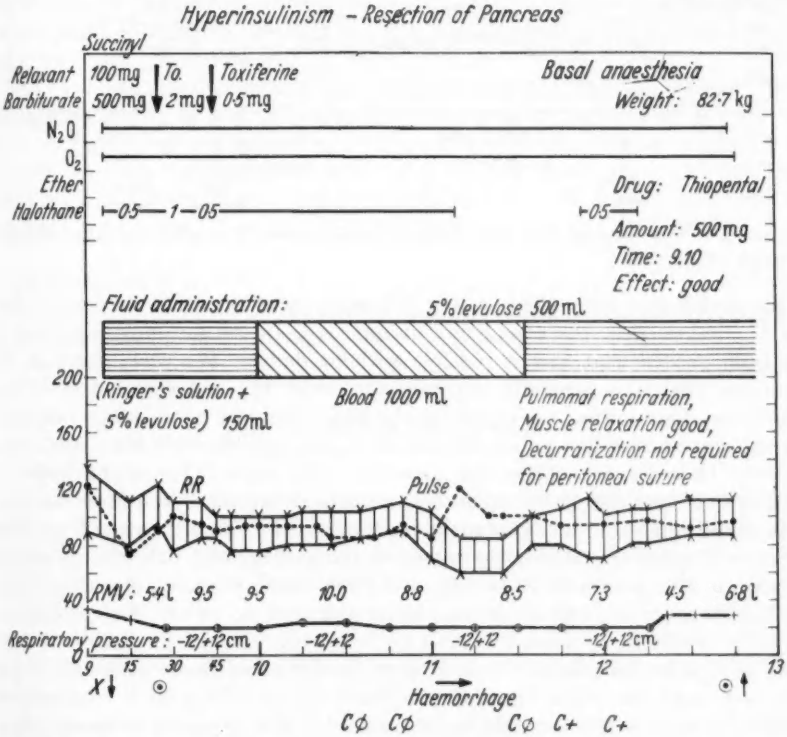

FIGURE 9. Anaesthetic data sheet showing long-lasting relaxation with Toxiferine in an operation for pancreatic tumor.

and never more. The duration of adequate muscle relaxation (to fulfill even the highest demands) after single injection of the aforementioned dose was 45 to 130 min. When increase of muscle tension or reappearance of spontaneous respiration began to interfere with the operation, we administered either ½ mg. Toxiferine or 1 to 2 mg. methylcurarine if the operation was still expected to continue for some time, and this provided further relaxation for a good hour, or in some cases even longer. There is no contraindication to the additional administration

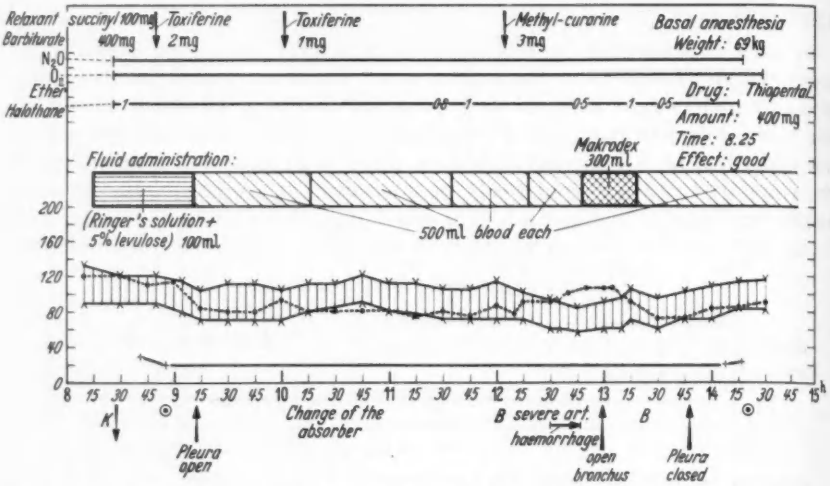

FIGURE 10. The anaesthetic data sheet showing combined use of Toxiferine and other relaxants for difficult lobectomy.

of succinylcholine for a short-lasting relaxation which may be necessary after the Toxiferine effect has completely disappeared. In our auto-investigations it has been proved that this is possible without danger. We wish, however, to point out that it is generally impossible to await the complete fading of the Toxiferine effect during the operation. In such cases, we occasionally observed that succinylcholine had an insufficient effect, or that relatively high doses were required in order to achieve the necessary relaxation. This might result in difficulties at the end of the operation, if the spontaneous respiration does not recur immediately and it cannot easily be determined to what extent the paralysis is due to Toxiferine and to what extent to succinylcholine. Although no serious consequences result from this—at most, the patient must receive artificial respiration after the end of the operation—we tend to follow the repolarizing relaxant Toxiferine by a small dose of the likewise repolarizing relaxant methyl-curarine if a second injection is necessary. In this case, we are certain of being able to reverse the effect. Or, if only a short-lasting relaxation is required, we prefer to inject only the amount of succinylcholine generally required for a sufficient relaxation. If this dose is ineffective, relaxation should not be forced by higher doses of succinylcholine. If worse comes to worse, one can try increasing the depth of anaesthesia.

For the maintenance of the anaesthesia, the aforementioned doses with the addition of a small amount of halothane (we generally administered only 0.5 per cent and never exceeded 1 per cent) had a longer and more even effect than nitrous oxide-oxygen alone. There seems to be a true potentiation. The possibility of easy hyperventilation typical of halothane anaesthesia is a particularly favourable feature as the effect of Toxiferine wears off and often avoids the necessity of a second injection.

Possibility of Being Antagonized

If decurarization is required, the following technique has proved to be appropriate: if only a slight residual curarization remains on the return of sufficient spontaneous respiration, the patient not yet being able to open his eyes completely and having difficulty in swallowing, intravenous injection of ½ mg. physostigmine following the administration of ¼ to ½ mg. atropine will rapidly abolish these slight residual effects. In case of more pronounced residual curarization, we gave an additional ½ mg. physostigmin or 5 mg. pyridostigmin intramuscularly. If sufficient spontaneous respiration had not been re-established at the end of the operation, we administered 1 mg. physostigmin intravenously following the intravenous injection of ½ mg. atropine. At our Toxiferine dosage, higher doses were never required to re-establish normal spontaneous respiration. In order to avoid recurarization which might be expected because of the relatively short-lasting effect of physostigmin, when compared with the duration of the effect of Toxiferine, we additionally administered 2.5 mg. pyridostigmin intravenously and 2.5 mg. intramuscularly. With this procedure we never observed recurarization. However, we always awaited the return of spontaneous respiration, even if only to a slight extent, before decurarization was performed.

Accidents or Deaths

To date, we have not observed any accidents or deaths which could have been attributed to the use of Toxiferine.

Discussion and Conclusions

Indications

(*a*) *Operations of long duration.* Because of its intensive and prolonged effectiveness, Toxiferine has proved to be excellent for protracted operations requiring strong, long-lasting, even muscle relaxation. In these cases Toxiferine can be used as the sole relaxant. Because it has no histaminic effects, there are no contra-indications to its use in allergic or asthmatic patients. For operations of unpredictable duration, Toxiferine can be used in low dosage as the basic relaxant and, if necessary, its effect increased by methylcurarine or another repolarizing relaxant.

(*b*) *Tetanus.* It so happened (it was, in fact, a happy coincidence) that at the time when Toxiferine was at our disposal we had only such mild cases of tetanus that no curarization was necessary at all. Thus, to date, we have had no opportunity to use Toxiferine in cases of tetanus, but we are convinced that it would be especially appropriate for such cases.

(*c*) *Neurological and rheumatic diseases.* Its even and long-lasting effect also justifies the attempt to use Toxiferine (subcutaneously in doses of 0.5 mg. to 1 mg.) in spastic diseases and contractures in the neurological field, as well as in rheumatic diseases, although, of course, in correspondingly lower dosage and under the supervision of an anaesthetist or physician who is experienced in the technique of intubation and artificial respiration.

Contraindications

(*a*) *Short operations.* As shown by our tests, the duration of the effect of Toxiferine depends to a considerable extent on the dose. Toxiferine in lower dosage could, therefore, also be used for shorter operations. There is, however, no point in this. For short interventions there are quite a number of very good short-acting relaxants which are easier to handle.

(*b*) *Myasthenia gravis.* Myasthenia gravis pseudoparalytica represents a true contraindication for any use of curare and therefore all the more for Toxiferine.

(*c*) *Disturbances of electrolyte and acetylcholinesterase metabolism.* As mentioned before, we are somewhat more reluctant to administer Toxiferine in cases with impaired liver function or in cases in which there is a tendency to haemorrhage from the very beginning or in which an increased parenchymatous haemorrhage might considerably disturb the operation. In severe disturbances of electrolyte and acetylcholinesterase metabolism, it is preferable to avoid the use of powerful and long-lasting relaxants.

Summary

The Calabash alkaloid Toxiferine is the most potent and long-acting relaxant of the curare group available to the clinic. As little as 2 mg. produces sufficient relaxation for all operative interventions in adults, of a marked degree for 30 minutes and slowly wearing off during the next 30 minutes.

As shown in 30 auto-investigations and 100 clinical cases, the drug is appropriate for muscle relaxation during operations of more than one hour duration. In addition, it is of value as a "basic relaxant" because it can be antagonized by Prostigmin and can be combined with other relaxants.

Only minor side-effects were observed: there was no marked histamine release or pronounced effect on blood pressure and pulse rate. There were no accidents or deaths among our cases.

Further clinical investigations of Toxiferine are justified, especially for long-lasting relaxation in cases of tetanus and neurological disease. Contraindications are: short-lasting operations; myasthenia gravis pseudoparalytica; disturbances of electrolyte and acetylcholinesterase metabolism.

Résumé

Les relaxants musculaires qui existent actuellement n'apportent pas encore toute satisfaction à l'anesthésiologiste en ce qui concerne la durée de leur action, la possibilité d'être inhibé par un antagoniste, et l'absence d'effets secondaires. C'est pourquoi il est justifié de poursuivre les recherches en vue de mettre au point de nouveaux relaxants.

L'isolement de la substance pure et la détermination de la structure chimique des alcaloïdes les plus importants extraits du Calabash-curare, par P. Karrer et H. Schmid, en 1958, ont éveillé le désir d'expérimenter la Toxiférine au point de vue clinique. Les premiers essais pharmacologiques et cliniques ont été réalisés par Waser et Harby. Au cours de nos recherches, la Toxiférine s'est avérée, par rapport à d'autres relaxants non-dépolarisants, ne provoquer que de

minimes effets secondaires de type histaminique. Le pouls et la T.A. ne sont pas notablement modifiés par des doses cliniques. L'action est plus marquée et plus prolongée que celle des alcaloïdes naturels du curare connus jusqu'à présent. Chez l'adulte, il suffit d'une dose de 2 mg pour produire une relaxation durant de 40 à 120 minutes, qui permet toutes les interventions. Chez le sujet conscient et bien portant, une dose de 1 mg entraîne une diminution moyenne de 50% de la capacité vitale et jusqu'à 10% de la force musculaire. La dépression de la capacité vitale est d'une durée très nettement plus brève (environ 20 minutes) que la diminution de la force de préhension (environ 40 minutes). Les sujets du sexe féminin et les débilités répondent à des doses ne dépassant pas 0,7 mg, de la manière précédemment décrite.

Cliniquement, ce médicament s'est avéré efficace dans plus de 100 anesthésies pratiquées par les auteurs. Il est indiqué comme relaxant (éventuellement comme relaxant de base) dans les interventions chirurgicales devant durer plusieurs heures. Il n'a pas été nécessaire de dépasser la dose de 3 mg, la plus élevée qui ait été utilisée jusqu'à présent, car la répétition des injections produit une véritable accumulation. On a également constaté que la Toxiférine pouvait être associée à la tubocurarine, à la diméthyl-d-tubocurarine, à la gallamine, etc., de même qu'à l'Halothane, si la concentration de ce dernier ne dépassait pas 0,5% de l'air destiné à être inspiré. Toutefois des études plus approfondies paraissent nécessaires dans les cas d'interventions chirurgicales majeures de longue durée requérant une relaxation prolongée (dans les cas de tétanus gravissime par exemple).

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THE INFLUENCE OF EXERCISE ON THE NEUROMUSCULAR ACTIVITY OF RELAXANT DRUGS*

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A RECENT SURVEY of the literature[1] revealed little information on the influence of exercise on the course of the neuromuscular block induced in man by quaternary ammonium-type relaxants. Consequently, observations on the effects of the rate of exercise on the partial neuromuscular block were included in a comparative study[2] carried out with five relaxants in unanaesthetized human subjects.

MATERIAL AND METHODS

This investigation was carried out in five male and five female healthy, adult volunteers. The relaxants studied were d-tubocurarine chlorine (d-Tc), toxiferine chloride (toxiferine),‡[3] gallamine triethiodide (gallamine), decamethonium bromide (ClO), and succinylcholine (SCh). In preliminary studies, the dose of each drug which produced a 90 to 95 per cent decrease of the grip strength, or a 50 to 55 per cent decrease of vital capacity, whichever was greater, was selected. The enzymatic hydrolysis of SCh was prevented by the intravenous administration of 0.3 mg./kg. of hexafluorenium,[4] a selective inhibitor of plasma cholinesterase. The doses of the relaxants studied are presented in Table I.

TABLE 1

THE DOSE OF THE RELAXANTS STUDIED

Compound	Dose microgm./kg.
d-Tc	100
Gallamine	700
Toxiferine	15
ClO	27
SCh*	80

*Administered five minutes after the intravenous injection of 0.3 mg./kg. hexafluorenium.

With one exception, two experiments were carried out with each of the five relaxants on all subjects. With toxiferine, however, one of the ten original subjects, who became unavailable before the termination of the study, was

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‡Toxiferine chloride was obtained through the courtesy of Dr. Leo A. Pirk of Hoffman-LaRoche Inc., Nutley, New Jersey.

replaced by another volunteer. Grip strength (measured by a dynamometer) was determined immediately before and after exercise consisting of the squeezing of the bulb of an ergograph* apparatus for one minute with the maximum effort of which the subject was capable, before and at three, six, and ten minutes after the start of the injection of the relaxant, and at five minute intervals thereafter. With each relaxant, the subjects exercised at the rate of six per minute on one occasion and at 60 per minute on another. Vital capacity, measured with a Bennett or Draeger ventilation meter, as well as blood pressure, pulse, and respiratory rate, were also recorded at appropriate intervals. The experiments, with a few exceptions, were carried out until grip strength returned to 75 per cent of control.

Results

There were marked differences between the effects of the non-depolarizing (d-Tc, toxiferine, and gallamine) and the depolarizing relaxants (ClO and SCh). The non-depolarizing relaxants affected grip strength much more than vital capacity. In contrast, there was relatively little difference in the effects of the

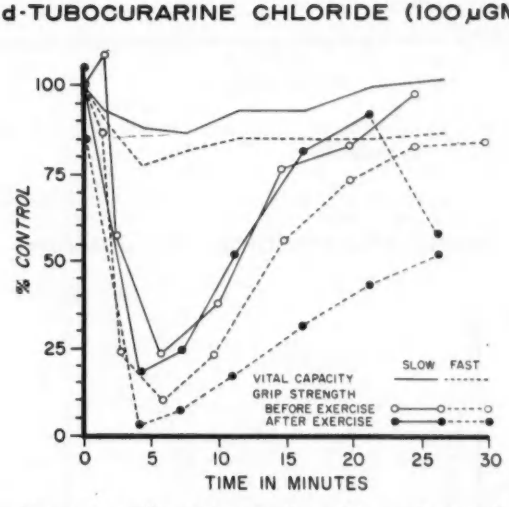

FIGURE 1. Effect of the rate of exercise on grip strength after the administration of 100 microgm./kg. d-Tc. The curves (also in Figures 2, 3, 4, and 5) represent the averages obtained in ten subjects.

depolarizing relaxants on grip strength and vital capacity. No significant difference was found in the magnitude of grip strength before and after exercise at a slow rate (six per minute) with either the non-depolarizing or the depolarizing relaxants. (See Figs. 1, 2, 3, 4, and 5.) After exercise at the fast rate, however, the grip strength at comparable times was significantly less after exercise if a

*Obtainable from Fred J. Christensen, Physiological Apparatus, Watertown, Massachusetts.

non-depolarizing relaxant was used (Figs. 1, 2, and 3). No such difference was found when the experimental subjects received a depolarizing relaxant (Figs. 4 and 5).

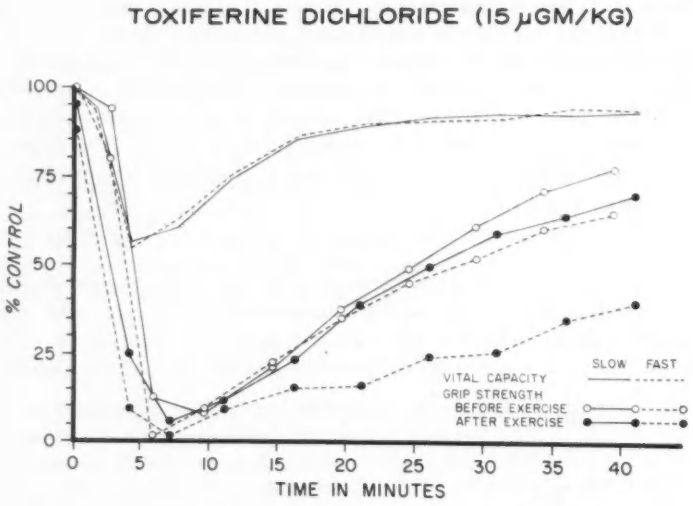

FIGURE 2. Effect of the rate of exercise on grip strength after the administration of 15 microgm./kg. toxiferine.

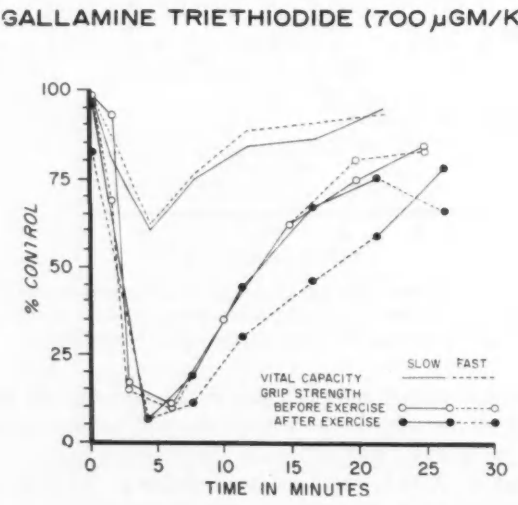

FIGURE 3. Effect of the rate of exercise on grip strength after the administration of 700 microgm./kg. gallamine.

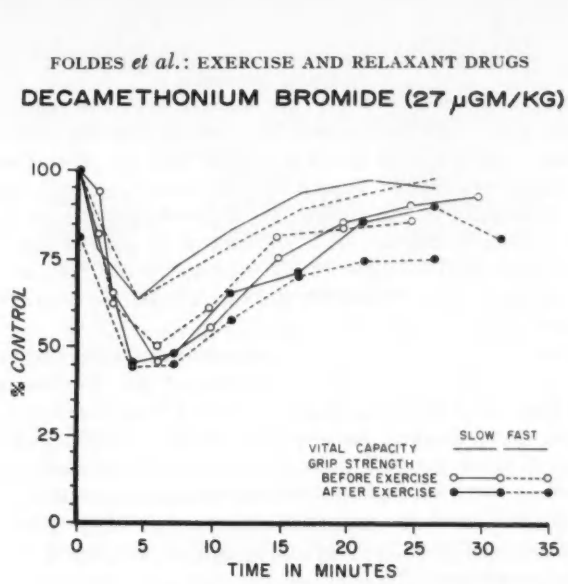

FIGURE 4. Effect of the rate of exercise on grip strength after the administration of 27 microgm./kg. ClO.

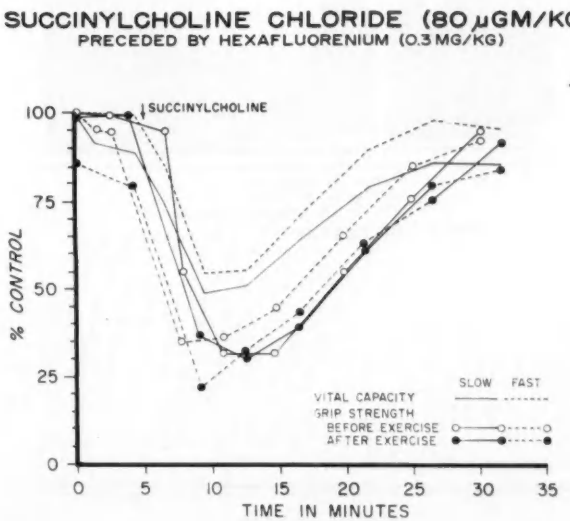

FIGURE 5. Effect of the rate of exercise on grip strength after the administration of 80 microgm./kg. SCh. All subjects received 0.3 mg./kg. hexafluorenium five minutes before the injection of SCh.

The difference in the effects of the rate of exercise on the grip strength after partial neuromuscular block produced by non-depolarizing and depolarizing relaxants is also evident from Figures 6, 7, 8, 9, and 10. After the use of non-depolarizing relaxants (Figs. 6, 7, and 8) with exercise at the rate of 60 per minute, there is a rapid decrease (fatigue) in the amplitude of the ergograph tracing. If the exercise is carried out at the rate of six per minute, there is little or no decrease in the grip strength during exercise. In contrast, with the use of depolarizing relaxants (Figs. 9 and 10) the rate of exercise does not affect grip strength (no evidence of fatigue).

Subjects who received non-depolarizing relaxants and exercised at a slow rate until grip strength returned to 75 per cent of control and then five minutes later exercised at a fast rate sustained a marked decrease in grip strength (Figs. 1 and 3). Under these circumstances, the grip strength was about the same as when they exercised at a fast rate all through the experiment. Conversely, if after exercise at a fast rate throughout the experiment, the rate of exercise was slowed to six per minute at the end, the "after exercise" grip strength increased markedly to about the level reached if the subjects exercised at a slow rate throughout the experiment (Fig. 3).

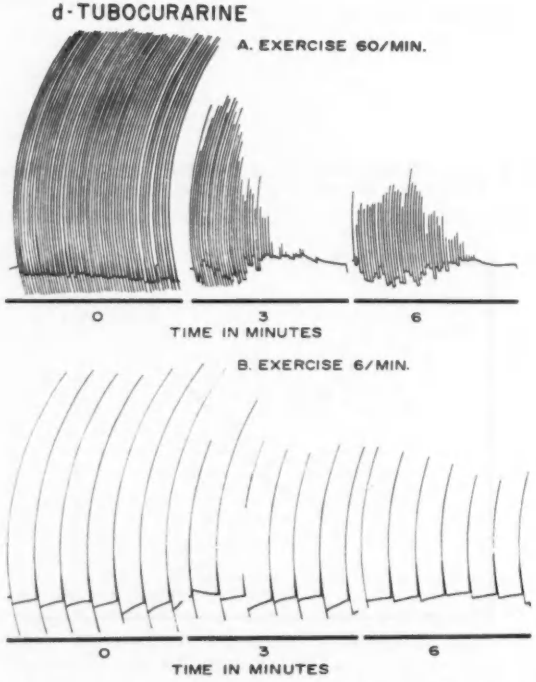

FIGURE 6. Ergograph tracings after the administration of 100 microgm./kg. d-Tc. Upper tracings, fast rate (note fatigue); lower tracings, slow rate (note absence of fatigue).

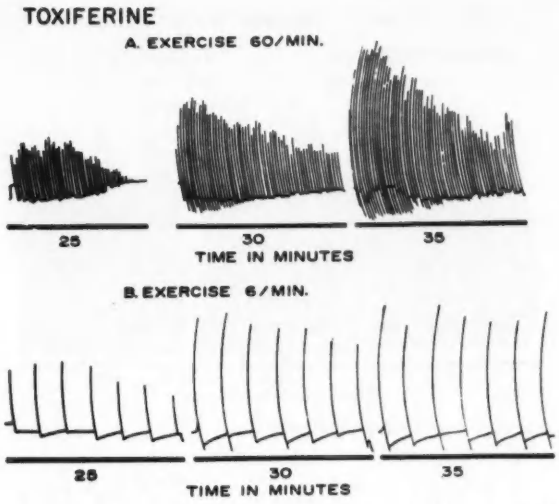

FIGURE 7. Ergograph tracings after the administration of 15 microgm./kg. toxiferine. Upper tracings, fast rate (note fatigue); lower tracings, slow rate (note absence of fatigue).

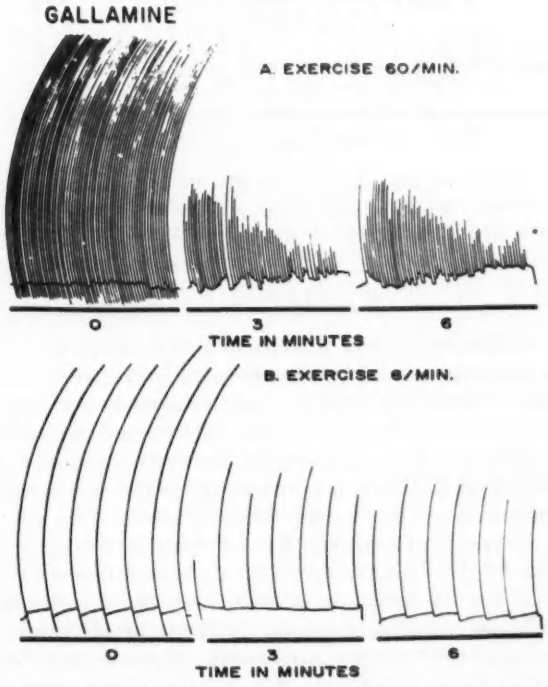

FIGURE 8. Ergograph tracings after the administration of 700 microgm./kg. gallamine. Upper tracings, fast rate (note fatigue); lower tracings, slow rate (note absence of fatigue).

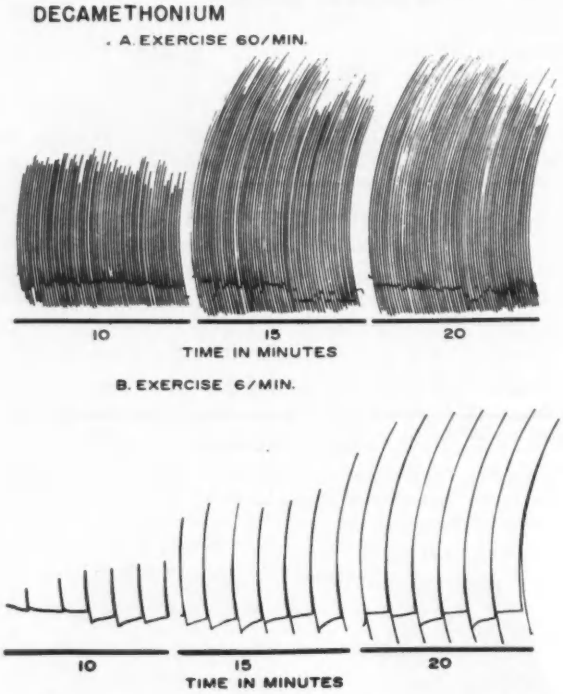

FIGURE 9. Ergograph tracings after the administration of 27 microgm./kg. C10. Upper tracings, fast rate; lower tracings, slow rate. Note absence of fatigue after exercise at fast rate.

COMMENTS

The findings of this study are in agreement with those of Schmidt and Chase[5] who found that previous exercise potentiated and prolonged the neuromuscular effects of d-Tc in rabbits. Both their findings and ours may be explained by the exhaustion of the acetylcholine reserves by exercise and a resultant decrease in the quantity of acetylcholine released by the nerve impulse at the endplate. Since acetylcholine and d-Tc are in competition for the cholinergic receptors of the endplate, decrease of the acetylcholine concentration will increase the effect of d-Tc. Although presumably the depolarizing relaxants also compete with acetylcholine for the cholinergic receptors,[6] the depletion of the acetylcholine reserves by rapid exercise does not intensify and prolong the neuromuscular block in man. The depolarizing relaxants, similar to acetylcholine, increase the "lability" of the endplate[7,8] toward depolarizing influences, and during a partial block produced by these compounds the endplate region may be reversibly depolarized by smaller quantities of acetylcholine. It is also possible that while non-depolarizing relaxants interfere with the synthesis or release of acetylcholine

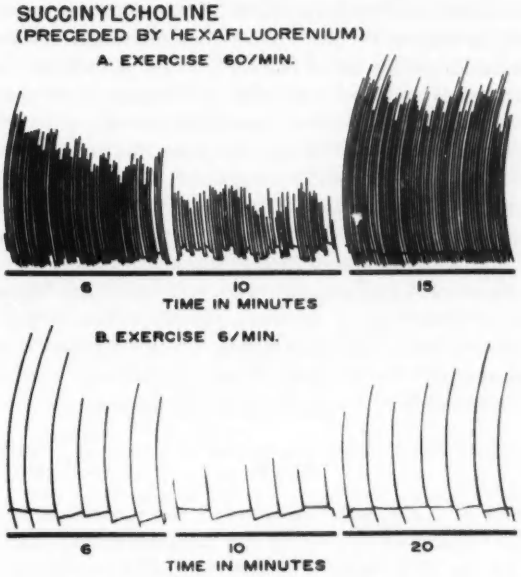

FIGURE 10. Ergograph tracings after the administration of 80 microgm./kg. SCh preceded by 0.3 mg./kg. hexafluorenium. Upper tracings, fast rate; lower tracings, slow rate. Note absence of fatigue after exercise at fast rate.

at the neuromuscular junction, the depolarizing relaxants interfere to a lesser extent or not at all with these mechanisms. Interference with the acetylcholine synthesis or release has been postulated as the cause of the neuromuscular block induced by hemicholinium.[9] It is of interest that the intensity of the hemicholinium block is also markedly influenced by the rate of stimulation.

With our experimental set-up, it was not possible to confirm the observation of Churchill-Davidson and Richardson[10] that exercise shortened the duration of the ClO induced neuromuscular block. There is a good agreement, however, between the recent findings of Churchill-Davidson and Christie[11] and the present findings. They observed in human subjects a gradual decrease in the amplitude of the electromyogram induced by repeated indirect stimulation during partial neuromuscular block caused by d-Tc. No such decrease in the height of the electromyographic tracing was observed if the partial neuromuscular block was induced by ClO.

Our findings also indicate that if the rate of exercise is six per minute or less, enough acetylcholine is released by the nerve impulse to maintain neuromuscular transmission at a constant level. It is also evident that the acetylcholine reserves, exhausted by rapid rate of exercise, recover within three to five minutes to the extent that there is no difference between the pre-exercise grip strength with slow or fast rate of exercise.

The influence of the rate of exercise on the partial neuromuscular block induced by non-depolarizing relaxants, besides its theoretical interest, may also have clinical significance. After the use of relaxant drugs, partial neuromuscular block is frequently present at the termination of anesthesia. After discontinuation of the assisted or controlled respiration, spontaneous respiratory activity may be seemingly adequate for a time. Later, however, the diaphragm may become exhausted, and if the patient is left unassisted, hypoxia and hypercarbia will develop. In extreme cases, fatigue of the partially "curarized" respiratory muscles may result in the patient's death. Anoxic deaths have been encountered in patients who had seemingly adequate spontaneous respiratory activity at the termination of the anesthesia and who were left under inadequate supervision. Since in man, on prolonged administration, the properties of the neuromuscular block induced by depolarizing relaxants may become similar to those caused by non-depolarizing agents,[12] the dangers of post-anaesthetic "recurarization" due to fatigue are also possible with non-depolarizing agents.

Summary

1. The influence of the rate of exercise on the partial neuromuscular block produced by three non-depolarizing (d-Tc, toxiferine, and gallamine) and two depolarizing (ClO and SCh) relaxants was studied in ten healthy, adult, unanaesthetized subjects equally divided between the two sexes.

2. Exercise, which consisted of squeezing the bulb of an ergograph at the rate of six per minute, had no effect on the partial neuromuscular block, as measured by the grip strength, produced by either non-depolarizing or depolarizing relaxants.

3. Similar exercise, but at the rate of 60 per minute, caused a rapid decrease of the grip strength if the partial neuromuscular block was induced by a non-depolarizing agent. No fatigue was observed under similar circumstances if the partial neuromuscular block was induced by a depolarizing relaxant.

4. Possible explanation of the findings presented and their clinical significance have been discussed.

Résumé

L'on a injecté par voie i.v. en 90 secondes, chez 5 hommes et 5 femmes adultes, bien portants, non anesthésiés, volontaires, du chlorure de d-tubo-curarine, du triéthiodure de gallamine, du chlorure de toxiférine, du bromure de décaméthonium et du chlorure de succinylcholine, aux doses respectives de 100, 700, 15, 27 et 80 micromg/Kg. L'injection de succinylcholine a été précédée de celle de 0,3 mg/Kg d'hexafluorenium, par voie i.v., un inhibiteur plasmatique sélectif de la cholinestérase. On a noté la capacité vitale, la force de préhension, la T.A., le pouls et la fréquence respiratoire avant et à divers intervalles après l'administration des curarisants. La force de préhension a été mesurée immédiatement avant et après exercice consistant à presser la poire d'un ergographe durant une minute, puis une fois 6 fois/minute, et une autre fois 60 fois/minute. Aux doses utilisées, la diminution maximum de la force de préhension a été de 100,

90, 65 et 55% avec respectivement la toxiférine, la gallamine, la d-tubocurarine, la succinylcholine et le décaméthonium. Les réductions correspondantes de la capacité vitale ont été de 45, 40, 12, 50 et 36% respectivement. La récupération de la capacité vitale et de la force de préhension se font de façon parallèle avec la succinylcholine et le décaméthionium. Avec les autres agents, la capacité vitale revient plus rapidement à la normale que la force de préhension. Cette dernière est revenue à 75% de sa valeur normale au bout de 15 min. avec le décaméthonium, de 20 min. avec la d-tubocurarine, la gallamine et la succinylcholine, et au bout d'environ 60 min. avec la toxiférine. Des exercices pratiqués à un rythme rapide intensifient et prolongent de façon très marquée les effets de la d-tubocurarine, de la gallamine et de la toxiférine, mais non ceux du décaméthonium et de la succinylcholine sur la force de préhension. Par contre des exercices pratiqués à un rythme lent sont demeurés sans effet.

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ANAESTHESIA WITH HYPOTHERMIA FOR OPEN HEART SURGERY IN CHILDREN*

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THE USE OF HYPOTHERMIC ANAESTHESIA to allow "open" heart surgery has become commonplace. The technique is simple and relatively safe and allows direct visual repair of the defect. Its major disadvantage is the limited time available. Therefore, this method is usually restricted to the correction of two types of defects: the atrial septal defect of the secundum type and valvular pulmonary stenosis. The first part of this paper deals with the management of 100 patients with an atrial septal defect, and the second part with 55 patients with valvular pulmonary stenosis. The pathology of each lesion will be briefly reviewed, followed by the anaesthetic management and our results.

ATRIAL SEPTAL DEFECT

Pathological Effects

Figure 1 shows the four main types of defects in the atrial septum viewed from the left side of the heart. Only defects of the ostium secundum type or those involving a patent foramen ovale are suitable for closure using hypothermia alone. Ostium primum defects and atrial ventricular communis defects require too much time for this method. Figure 2 shows a typical secundum type defect.

Figure 3 is a diagrammatic presentation of the haemodynamics resulting from this lesion. With an intact septum the left atrial pressure is 5 mm. higher than the right atrial pressure. With a small A.S.D., there is a pressure gradient of approximately 3 mm. of mercury, producing a left to right shunt. With larger defects the pressure difference is abolished, but a left to right shunt persists. The pulmonary blood flow may increase from two to four times that of the systemic system. The right ventricle adapts well to such a work load over many years and the pulmonary pressures may be only slightly elevated. Ultimately, the right ventricle fails, as a result of either the excessive work load or the development of increased pulmonary vascular resistance. As the right ventricle fails, the right atrial pressure rises and a right to left shunt may develop, producing cyanosis. At this stage the operative risks are very great.

Prognosis

Without operation these patients have an uncertain future. Deaths from A.S.D. in infancy are rare and serious symptoms infrequent before the age of

*This paper was presented at the Second World Congress of Anaesthesiologists, Toronto, Canada, Sept. 4–10, 1960.

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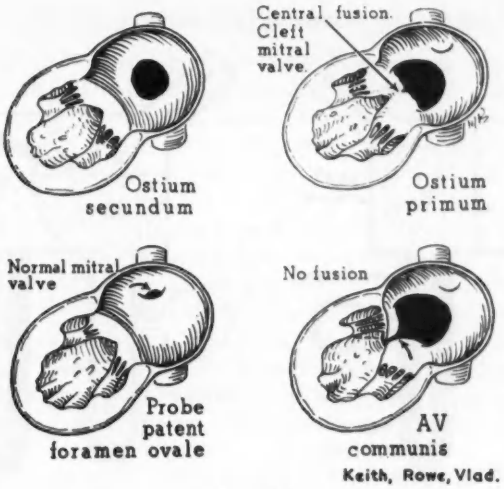

FIGURE 1

FIGURE 2

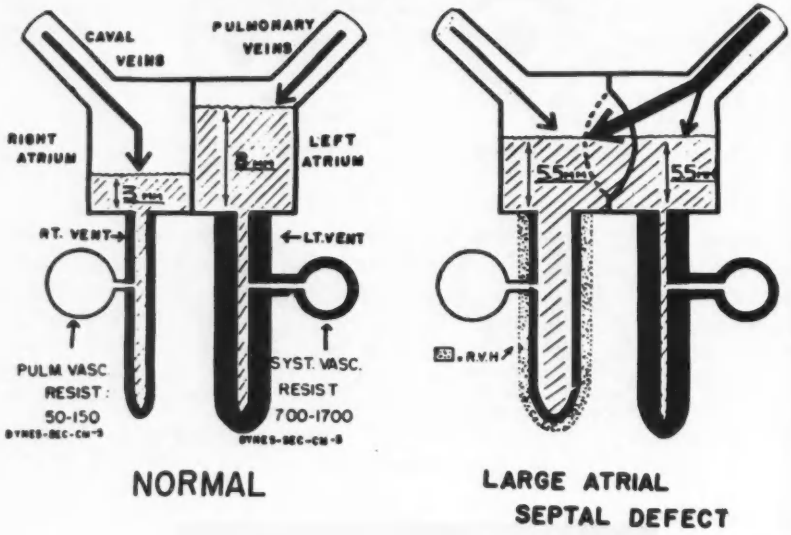

FIGURE 3

20 years. However, by 40 years of age, half the patients have gross cardiac enlargement and the average age at death is 49 years. Therefore, it is advisable to repair the defect at any early age. The age group two to ten years carries the least risk because this group have not had time to develop serious complications and the defect is still small and readily repaired.

Anaesthetic Management

The anaesthetic management begins with the preoperative visit.[1] Because this procedure is always elective in children, any complicating illness results in cancellation of the operation. The patient is thoroughly examined with special attention to the cardiovascular system. If no contraindications exist, premedication is ordered one hour preoperatively as follows:

1. Under 20 lb. atropine (0.012 mg./lb.) only.
2. 20–80 lb. atropine (0.012 mg./lb.) and meperidine (0.75 mg./lb.) and pentobarbital (1 mg./lb.).
3. Over 80 lb. atropine (0.012 mg./lb.) and morphine (0.1 mg./lb.).

The methods of induction of anaesthesia vary with the size of the patient and the severity of the cardiovascular lesion. In infants, cyclopropane and oxygen may be used followed by intramuscular succinylcholine (2 mg./lb.). If very seriously ill, succinylcholine with oxygen only is to be preferred. For the induction of babies and children, 2½ per cent thiopentone ("sleep" dose) followed by intravenous succinylcholine (1 mg./lb.) is satisfactory. After oxygenation, intubation is performed with a Portex Magill tube. After intubation anaesthesia is

maintained with nitrous oxide-oxygen until spontaneous respirations return. During cooling, nitrous oxide-oxygen-halothane (0.5 to 1 per cent) is used. During surgery, until the occlusion period, hyperventilation is maintained and nitrous oxide-oxygen-halothane is supplemented by additional succinylcholine as needed. After occlusion, hyperventilation is maintained with nitrous oxide-oxygen only.

For maximum safety during this type of surgery, various physiological functions must be monitored. In particular, the cardiovascular system must be closely checked. In addition to an oesophageal stethoscope and an oscillometer, we use a six-channel Sanborn machine with visoscopes for obtaining an electrocardiogram, electrocephalogram, and direct pressure recordings. Blood loss is measured by using calibrated suction flasks, weighing of sponges, and estimating the blood loss on drapes. Administered intravenous fluid is accurately measured. All data is charted concurrently on a blackboard to maintain an exact report on blood balance.

Hypothermia

Patients are surface cooled by using a "Therm-O-Rite" blanket with fluid circulating at 0° C., and ice-bags are placed over the axillary and inguinal areas. Patients over 75 lb. may have small amounts of ice placed directly on the skin to increase the rate of cooling. Surface ice should be used cautiously as it greatly increases subsequent drift of temperature. When temperature is below 33° C., movements of the patient should be minimal to avoid undue stimulation of the hypothermic heart. Oesophageal, rectal, and muscle temperatures are recorded every ten minutes.

The rate of cooling cannot be accurately predicted because of the numerous factors involved, such as size of patient, degree of muscle tone, amount of peripheral vasoconstriction or dilatation, amount of adipose tissue, the ambient temperature and humidity including the use of ice, and individual variation. The most reliable guide to subsequent temperatures is indicated by the slope of the temperature curve. As the slope steepens, cooling must cease somewhat earlier because of increased drift. When cooling is rapid, the oesophageal and rectal temperatures may differ by several degrees, with the oesophageal temperature usually being lower.

What is the optimal temperature for occlusion and repair of atrial septal defects? There are numerous points to consider but the time factor is the most vital one. In our series, the average time for repair of the first 75 cases was 4.8 min., but in the last 25 cases was 3.9 min. However, the occlusion period ranged from 2 to 7½ min. It is necessary to allow a maximum period of occlusion even if operative time is somewhat increased. Thus the optimal temperature is 30° to 31° C.

Rewarming is instituted according to the slope of the temperature curve and the stage of the procedure. The warming solution is circulated at 40° C. and hot water bottles may be added. When the rectal temperature reaches 33° C., the patient may be awakened and returned to the recovery room.

Within the moderate range of hypothermia used in this series, complications ascribed to hypothermia were rare. These may be mentioned as follows.

(1) Increased myocardial irritability. Eleven cases developed ventricular fibrillation but all of these occurred immediately after the occlusion period and four cases had visible coronary air emboli. Many factors other than hypothermia were involved.

(2) Alterations in bleeding and clotting times. No haematological investigations were performed in this series but haemorrhage was not a troublesome feature, except during the occlusion period.

(3) Metabolic acidosis. In adults undergoing hypothermia, an "acute acidotic syndrome" has been described during rewarming. None of our patients developed this complication. A study of the acid-base and electrolyte changes in some of our patients showed only minor alterations.

Occlusion Period

Before the heart is occluded, several steps must be taken.

(1) Blood loss must be determined and balanced. Then a 500 cc. bottle of heparinized blood must be started intravenously. This bood is administered to replace losses occuring during the occlusion.

(2) A flow of CO_2 (6 L/min) is started and connected to an "ether hook" at the operative site. This gas blankets the left atrium to avoid air emboli.

(3) Succinylcholine is injected to prolong the apnoeic phase.

(4) 100 per cent oxygen is administered for 30 sec. preceding occlusion.

During the occlusion period, additional steps must be taken.

(1) Gas flow is cut off and the lungs are allowed to collapse.

(2) The duration of occlusion is announced at two-minute intervals.

(3) As the final suture in the defect is tied, the lungs are inflated, forcing out blood which fills the left atrium and displaces any air present.

(4) Blood lost is replaced but if the loss exceeds 300 cc. a search must be made for an unrecognized left superior vena cava, a loose caval tourniquet, or a distortion of the heart producing aortic valve insufficiency.

Within one minute of the restoration of the circulation, there is a marked rise in the systolic and diastolic blood pressures, sometimes reaching 230/130. During the subsequent 10 to 40 min., there is a gradual fall to normotensive levels. This hypertensive phase always occurs to some degree unless extreme hypovolaemia exists or gross myocardial failure is present. This has been called the post-occlusion hypertensive phase and has been studied in conjunction with Dr. R. A. Millar of Montreal. He determined the catecholamine levels present during this phase and they exactly parallelled the hypertensive phase.[2] It appears that the adrenal glands are stimulated to secrete epinephrine and norepinephrine during this phase, but the exact mechanism has not yet been determined.

Results

This paper deals with 100 consecutive paediatric cases which were diagnosed as having uncomplicated atrial septal defects of the secundum type. They came to operation during the period January 1957 to April 1960. The ages ranged from 4 to 16 years and are subdivided according to Table I.

The ratio of females to males was 60/40 which tends to confirm a slightly increased incidence in females.

TABLE I

	4–7 yrs.	8–11 yrs.	12–16 yrs.	Total
Male	15	15	10	40
Female	28	19	13	60

Complications (deaths: 2 per 100 cases).

(1) September, 1957, an eight-year-old patient, 24 hours postoperatively, developed mediastinal tamponade followed by a cardiac arrest. Resuscitation was unsuccessful; lungs had gross intrabronchial and intra-alveolar haemorrhage.

(2) September, 1959, a 14-year-old patient had an incomplete closure of A.S.D. in March, 1957. At second attempt a 3-inch hole was torn in the right atrium and 7 L. of blood was lost. Resuscitation was successful but the operation was postponed. During rewarming, cardiac arrest occurred. When again resuscitated, cooling was reinstituted, and A.S.D. closed. Subsequently, the heart would not maintain its contractility.

Complications (*morbidity*: 29 *per* 100 *cases*). Cardiac arrythmias: 11 patients developed ventricular fibrillation after occlusion, 4 patients developed other serious irregularities; air emboli: 4 patients had visible coronary air emboli; 5 patients had evidence of cerebral disturbances, probably air emboli; blood loss: 10 patients lost over 1,000 cc. during occlusion; infection: 3 mild and 1 severe case; technical difficulties: 4 multiple defects, 3 associated anomalous pulmonary veins, 1 dextroposition, 1 incomplete closure, 1 thoracotomy only.

Valvular Pulmonary Stenosis

This defect is corrected by occluding the heart, opening the pulmonary artery, and incising the pulmonary valve. This procedure is named after Henry Swan who first reported it in 1954.

Congenital stenosis of the pulmonary valve is due to a fusion of the cusps which may be partial or almost complete (Fig. 4). The pathological changes are entirely the result of this obstruction to the outflow of blood from the right ventricle. The right ventricular pressure is greatly increased and may exceed systemic levels. The right ventricle hypertrophies and later undergoes dilatation and failure. The right atrial pressure also rises and in the presence of a patent foramen ovale, a right to left shunt may occur (Fig. 5).

Prognosis

Without valvotomy the prognosis depends entirely on the degree of stenosis. The more complete the stenosis, the earlier cyanosis and R.V. of atrium occur. Infants with a pin-hole orifice may develop cyanosis and failure and die in the first weeks of life. Patients with moderate degrees of stenosis may survive to middle age.

Anaesthetic management

The anaesthetic management for these cases is identical with that for atrial septal defects. The optimal temperature for this procedure is 31° to 32° C,. as the occlusion period is shorter. The average occlusion time in our cases was 3.2 min.

stenosis of pulmonary valve

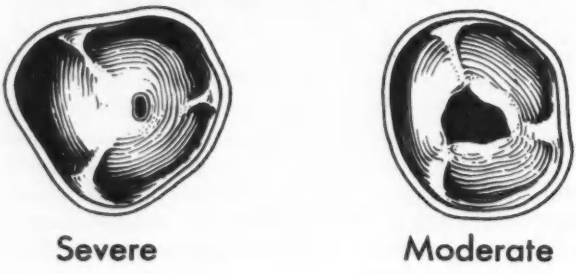

FIGURE 4

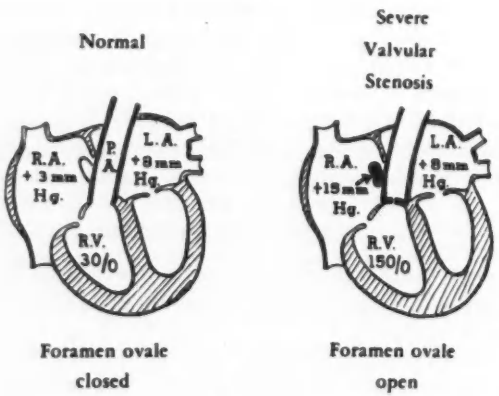

FIGURE 5

Results

TABLE II

	0–6 mos.	6 mos.–7 yrs.	8–16 yrs.	Total
Male	6	12	8	26
Female	7	14	8	29

Complications (deaths: 6 per 55 cases).

Age	*Time of death*	*Post-mortem findings*
20 days	7 hrs. postop.	Pulmonary atresia, small R.V.
10 weeks	8 hrs. postop.	V.S.D., infundibular pulmonary stenosis, small R.V.
8 days	24 hrs. postop.	Infundibular pulmonary stenosis, hypoplastic R.V.
10 days	5 hrs. postop.	Tricuspid hypoplasia, small R.V., mediastinal tamponade
21 days	14 hrs. postop.	Tricuspid hypoplasia, small R.V. pulmonary atresia
4 mos.	D.O.T.	Tricuspid atresia, pulmonary atresia.

These infants all came to operation with cyanosis and cardiac failure and were unresponsive to medical therapy. In some, there was no time for cardiac catheterization and exact diagnosis. The risks of such a major procedure to a moribund infant must be accepted. With more knowledge and experience, and infinite attention to detail, the operative mortality in these tiny infants will be reduced.

Complications (morbidity: 16 per 55 cases). Ventricular fibrillation, 11; arrythmias, 1; blood loss over 1,000 cc., 1; wound infection, 1; haemothorax, 1; atelectasis, 1.

Once the stenosed valve is incised and the circulation restored, these patients are dramatically improved. If no other lesions are still present, morbidity should not exceed that of thoracotomy.

Summary

The pathological features, the anaesthetic management, and the results of operation on 100 children with atrial septal defects and 55 children with valvular pulmonary stenosis have been discussed. These operations were carried out at the Hospital for Sick Children, Toronto, using anaesthesia with hypothermia only. This technique is simple and safe and allows direct visual repair for these defects.

Résumé

L'anesthésie sous hypothermie en chirurgie «à coeur ouvert» est entrée dans la pratique quotidienne. A l'«Hospital for Sick Children» de Toronto, cette méthode est utilisée essentiellement pour la correction de (a) défauts du septum auriculaire d'origine secondaire, et (b) la sténose des valvules des artères pulmonaires.

Cette communication s'appuie sur une série de 100 cas de fermeture de la communication inter-auriculaire, et de 60 cas de correction de la sténose des valvules pulmonaires.

On décrit les aspects anatomiques, physio-pathologiques et pronostiques de ces deux types de lésions cardiaques congénitales.

On discute ensuite de la conduite de l'anesthésie, y compris la préparation pré-opératoire, l'induction, le maintien et le contrôle.

On expose les méthodes utilisées pour refroidir et réchauffer les patients, ainsi que les complications de l'hypothermie.

On décrit et discute les problèmes qui se posent avant, pendant et après la période occlusive.

On expose enfin en détail les complications et les résultats de la correction de ces cas de lésions congénitales cardiaques.

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PULMONARY VENTILATION AND HYPOXIA*

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HYPOXIA, which is present in some patients with lung disease, may arise for the first time during a surgical operation; it can be inflicted upon an individual with normal lungs or superimposed by the anaesthetist upon one suffering from advanced lung disease.

To recognize the dangers before they develop is better than to have to counter them as they arise. Therefore, a system is desirable for revealing elements of pulmonary disorders likely to result in oxygen deficiency. Anaesthetists should find interest in such a system and in newer methods for testing the functions of the lungs upon which this is based.

HYPOXIA DUE TO PULMONARY DISEASE

Problems of conducting anaesthesia in patients with lung disease may be resolved, at least in part, by knowing which functions are upset and to what extent; this particularly applies to some of the commoner disorders. Unfortunately, physicians use the terms "chronic bronchitis," "asthma," and "emphysema" without general agreement. The phrase "chronic non-specified lung disease" has therefore been suggested for the group as a whole.[1] This includes patients with chronic‡ cough and expectoration, together with paroxysmal or persistent dyspnoea. The group excludes localized lung disease and generalized specific or infective diseases (for example, pneumonia, pneumoconiosis, collagen diseases, or primary cardiovascular renal disease).

Further differentiation of the non-specified group is made possible by lung function tests. Some of these may reveal abnormalities before clinical signs and symptoms appear; and some are simple enough for practical use.

LUNG FUNCTION

The "capacities" are not strictly tests of lung function; they roughly reflect the size of the patient and can be predicted from the height. Reduction in vital capacity (V.C.) occurs with diseases characterized by lesions encroaching upon the available space within the thorax, or which alter its shape, like kyphosclerosis. These "restrictive" disorders, since they diminish functioning lung tissue, are bound in one way or another, sooner or later, to affect respiration and inhalational procedures.

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‡By chronic is meant symptoms occurring on most days for at least three months in the year for at least two years.

"Obstructive" elements in the lower air passages can be as great a trial to the anaesthetist as obstruction in the upper airway. The vital spirogram gives measurements of both "restrictive" and "obstructive" disorders.[2] For this test a spirometer is needed which will not be affected by inertia or vibration in the fluid column. The instrument designed by Bernstein *et al.*[3] overcomes these disadvantages by having a double pulley system for suspension, a light weight ball of reduced length, a wide bore breathing tube, and a reduced water surface. A record of time in seconds is also required.

The patient is asked to inhale as deeply as he can from the air and then exhales as deeply and as fast as he is able into the spirometer. (The forced vital capacity [F.V.C.] which is measured in this way is for all practical purposes the equivalent of the V.C.) That fraction of the V.C. which can be expelled in a given time (0.75 or 1 sec.) is termed the forced expiratory volume (F.E.V.). This test can be more easily applied than the maximum breathing capacity (M.B.C.) to which it is related ($F.E.V._{1.0} \times 35 = M.B.C.$ in Litres or $F.E.V._{0.75} \times 40 = M.B.C.$).

A normal subject can exhale 80 per cent of his V.C. in one second; a patient with obstruction in the lower air passages may only be able to exhale 40 per cent. If the F.E.V. is markedly increased after the inhalation of bronchodilator drugs (adrenalin and atropine compound spray, 1 per cent isoprenaline, or 2.5 per cent phenylephrine hydrochloride) for two minutes, then it would be reasonable to assume that the obstruction is due to muscular spasm such as occurs in asthma. An efficient nebulizer should be used and the test should be repeated one minute later.

Wright[4] has devised an ingenious device which measures the peak flow of expiration. When this value is compared with the F.E.V., a very rough approximation between the two is found;[5] unfortunately, some patients with obstructive disorders are able to exhale for a short period at a high velocity.

These tests do not, by themselves, allow of a specific diagnosis. A disorder characterized by a reduced V.C. with a normal F.E.V. indicates a restrictive process such as pleural effusion, a carcinoma, a pneumothorax, a pulmonary fibrosis, or a kyphosclerosis. A normal V.C. with a reduced F.E.V. unaffected by bronchodilator drugs suggests an obstructive process like emphysema.

The forced exhalation ratio $\frac{F.E.V.}{V.C.}$ changes in patients with respiratory disease but is unchanged in those with breathlessness of cardiac origin.[6]

It used to be held that the ratio of the functional residual air (F.R.C.) volume to the total lung volume (T.L.C.), expressed as a percentage, could be used as a measure of the severity of emphysema.[7] Since emphysema cannot be defined precisely during life, this relation cannot be put to the test; furthermore, there is no linear relation between the ratio and the reduction in oxygen saturation of arterial blood in patients with pulmonary disease.[8]

A simple test is to cause the patient to step up and down a height of 20 cm. for two minutes at the rate of 30 times over a period of one minute (timed by metronome), and then to observe whether there is either cyanosis or breathlessness. An alternative procedure for a patient in bed is to cause him to raise and lower his legs with the knee joints extended at the rate of 60 times per minute

for two minutes. Undue breathlessness or cyanosis may suggest a diffusion defect in the lung and more complicated procedures like the carbon monoxide diffusion capacity are indicated.

If the patient is cyanosed at rest and the cyanosis remains after the inhalation of 100 per cent oxygen, then it may be assumed that there is a venous to arterial shunt. An oximeter is a better guide than relying upon visual impressions because, as Comroe and Botelho[9] showed, clinicians may not recognize a state of cyanosis until the arterial blood is only 70 per cent saturated with oxygen. Intrapulmonary shunts may result from direct venous to arterial channels which have developed as a result of infective processes.[10] When the disease process has developed so far as to cause respiratory failure, a raised carbon dioxide tension (pCO_2) can be measured. The normal range of pCO_2 is 40 mm. Hg, plus or minus 5 mm. Hg; 47 mm. Hg is considered the upper limit.

For many years pCO_2 measurements remained the province of respiratory physiologists because the methods were time-consuming and difficult. Recently a method has been introduced[11] and modified[12] so that pCO_2 can be measured with simple apparatus, and, furthermore, it comes within the capabilities of the resident anaesthetist or medical officer: to carry it out takes less than ten minutes.

The difference between the pCO_2 of mixed venous and arterial blood is 6 mm. Hg in the subject at rest[13] and this difference remains even in the presence of pulmonary disease. The aim of the test is to measure the mixed venous pCO_2. Subtracting 6 mm. Hg from this value gives an estimate of arterial pCO_2. The subject breathes into a half-gallon bag filled with oxygen or air for one and a half minutes. At the end of this time the contents of the bag are nearly in equilibrium with the mixed venous (pulmonary artery) pCO_2. After a two-minute rest, the subject breathes into the bag again for 15 sec.; at the end of this time the bag pCO_2 is identical with the pCO_2 of mixed venous blood. If the 15-sec. period is exceeded then there is a further accumulation of CO_2 from a recirculation. The error of this method is of the order of 3 mm. Hg. Although erroneous results occur when there is a large intracardiac shunt, the method is reasonably accurate in the presence of pulmonary disease.

Moran Campbell[14] has modified Haldane's apparatus to facilitate the measurement of pCO_2 and this has been achieved by removing the temperature compensatory burette and, instead of having to raise and lower the mercury bulb by hand, a syringe is used; all the operator has to do is to raise and depress the syringe barrel about fifteen times.

Hypoxia manifested during Operations due to Pulmonary Disease

Pathological lesions likely to influence anaesthesia are destruction of lung tissue, cyst formation, replacement of lung tissue by fibrosis, and reduction or thickening of the alveolar membrane.

Destruction of lung tissue reduces the extent of the vascular bed and eventually results in pulmonary hypertension. This leads to cardiac failure (cor pulmonale). Reduction in the extent of the alveolar membrane produces a diffusion defect. Where there are irregular patchy areas of lung destruction there may be some

alveoli without a vascular supply although they may be ventilated; this leads to an increase in the physiological deadspace; if alveoli are perfused but not ventilated then there is a venous admixture. Loss of supporting tissues around the bronchioles may result in airway obstruction during expiration, especially when expiration is an active process as may be the case after air trapping. Air trapping may occur when air passes into cystic areas of destroyed alveoli with valvular openings as described by Reid.[15] Air may also be trapped distal to obstructed air passages. Replacement of lung tissue by fibrosis will result in a reduction of the capacities and will lower the reserve volumes. Restrictive disorders affect the rate at which gases are exchanged and hypoxia, when it appears, does so rapidly. Thus there is less time available for intubation and hypoxia develops fast during respiratory spasm.

Patients with obstructive diseases like chronic bronchitis and emphysema would be expected to develop respiratory spasm more easily because of the unduly sensitive state of the bronchi, and they are more likely to develop hypoxia from the obstructive effects of secretions which have not been coughed up. In some patients respiration is only maintained by a hypoxic drive and these present the anaesthetist with problems which may become acute in the immediate post-operative period. For instance, it is difficult to ascertain the extent to which suboxygenation may be allowed.

When there is an increase in the physiological dead space this must be allowed for in assessing the correct amount of increased artificial ventilation volumes.

In restrictive disease the inhalation of oxygen for a few minutes before anaesthesia is induced is a wise precaution. Speed in intubation comes from skill and adequate preparations.

The use of intermittent positive pressure (I.P.P.) techniques are preferable to techniques with spontaneous respiration because the effect of positive pressure is to open up alveoli which were previously closed; at least this appears to be the case from the work of Motley and Tomashefski[16] in patients with pulmonary fibrosis. They showed how the oxygen difference between the alveoli and the arterial blood (Aa difference) decreased and the arterial oxygen tension rose with the patient breathing air with I.P.P. respiration to a value higher than it was when the patient breathed a high oxygen concentration spontaneously. Reducing the oxygen of inspired gases reduced the Aa difference; increasing the oxygen increased the difference.

In obstructive non-specific pulmonary disease it is important that the technique be arranged so that the upper airway is secure and all procedures and agents, such as ether and cyclopropane, likely to evoke spasm, should be avoided. To prevent any straining, the author's practice is to give the longer-acting relaxant before the patient begins to breathe as the effects of the short-acting relaxant (suxamethonium) wear off. Although contrary to current teaching, because of the danger of persistent curarization, this ensures a smooth transition without any straining.

Under full curarization there should be no active expirations and so air trapping from this cause is unlikely except during the recovery period as muscular power returns. Intermittent positive pressure respiration has much to

commend it in patients with pulmonary disease having surgical operation under anaesthesia, and not the least of the arguments in favour is that the patient can be well ventilated. If a negative phase is employed during expiration this should be used with care; in some instances hypoxia will develop because the thorax ceases to expand, presumably from air trapping during the positive phase.[17] Mixtures of helium and anaesthetic gases are rarely used in these patients.

Hypoxia due to Anaesthesia

Using the wrong gas in place of oxygen is now fortunately rare, but although there is a dual supply on every anaesthetic machine, it is still possible for the cylinder to become empty and for the anaesthetist to fail to realize it. With spontaneous breathing the odds are that the anaesthetist will notice the decrease in the bag size, but with artificial respiration with a pulmoflator, the error may not be so obvious and the patient may receive many respiration with pure nitrous oxide. There are devices (such as the Bosun)* which will sound an alarm when the oxygen runs out, but unfortunatly the anaesthetist may have forgotten to set the instrument into action.

The use of profound respiratory depression from the anaesthetic agent is likely to add the histotoxic form to anoxic anoxia and this combined state is most undesirable. Anaesthesia with spontaneous respiration increases the liability of anoxic anoxia, but this is to some extent avoided by the use of high oxygen mixtures as when halothane is used. Whatever form the respiration takes, it is desirable for the anaesthetist to know the extent of the respiration volumes, and there are a number of devices[4,18] to assist him.

Although the tidal and minute volumes can be readily measured, it is less easy to estimate alveolar ventilation, which is much more important. This is computed by subtracting the dead space (anatomical and physiological, whichever is the larger) from the tidal volume. The dead space is altered by intubation and by anaesthetic equipment.

An example of the way in which the dead space is affected by intubation may be taken from the case of a man with a 2-cm. diameter trachea which is 10 cm. long. Assume that the lower end of the tube reaches the mid-point of the trachea, then the dead space will amount to that volume contained in the tube (15 ml.), half the trachea (15 ml.), and the air passages below the carina. (Rohrer[19] computes this to be of the order of 70 ml.) Thus the dead space will amount to some 100 ml. With the patient breathing air through the upper end of the tube, the dead space would be reduced by some 50 ml. if it be assumed that the man's anatomical dead space is 150 ml. (Such would be the case in a man weighing 150 lb.) In anaesthetic practice, however, the upper end of the tube would be connected to a circle CO_2 absorption apparatus with an additional dead space of about 10 ml. A mask and a circle system would add 160 ml.; a mask and a Water's canister would add some 230 ml. (if the volume to the absorbing soda lime surface is reckoned at 80 ml.); a Water's soda lime canister without a mask would add some 80 ml. In the light of these findings it is interesting to compute

*Obtained from the British Oxygen Company Ltd., Deer Park Road, London.

the possible alveolar ventilation in a man inhaling oxygen and cyclopropane without intubation. If the patient's dead space is reckoned at 150 ml., then the total dead space will be of the order of 380 ml. If the tidal volume is depressed below the normal lower limit of 350 ml., then the alveolar ventilation will be 30 ml. multiplied by the respiratory rate; even if this were as much as 20/min., then the alveolar ventilation would only amount to 0.6 L./min. which is a marked reduction from the normal lower limit of about 3.5 L./min.

In some pulmoflators, provision is made so that the whole of each expiration is removed without rebreathing and without CO_2 absorption; in this type of equipment the increase of dead space due to the apparatus would amount to about 10 ml. only.

What happens to the physiological dead space during anaesthesia is more difficult to compute. Work in our own department[20] has shown that there is a difference between the pCO_2 in arterial blood and in alveolar air during anaesthesia with either spontaneous or artificial respiration. This order of difference (5 mm. Hg) was not found in conscious subjects where there is a difference of less than 2 mm. Hg which is almost within the error of the measurements. Other workers[21,22] have confirmed that this gradient exists which suggests that there is an increase in the physiological dead space during anaesthesia.

Diffusion anoxia[23] after nitrous oxide and oxygen anaesthesia may be countered by close supervision and efficient oxygen therapy in the immediate recovery period. The anoxia is intensified by an outpouring of secretions as might occur when neostigmine has been given after insufficient atropine at the end of operation.

The hypoxic dangers of respiratory spasm are becoming less with the increasing use of relaxant techniques or those which include non-irritating agents such as halothane.

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ANAESTHESIA AND PULMONARY EMBOLISM*

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THIS REPORT is a review of 105 autopsy-proven cases of postoperative pulmonary embolism, which occurred during the four-year period, July 1, 1955, to June 30, 1959, at the Vancouver General Hospital. Pulmonary embolism was the sole cause of death or a major contributing cause in each of the 105 cases.

RESULTS

Incidence of Death from Pulmonary Embolism in the Postoperative Patient

Proof of pulmonary embolism can be obtained only at autopsy. However, it is of interest that Israel and Goldstein,[1] in a review of hospital clinical diagnoses, found pulmonary embolism to be more frequent than either pneumonia or bronchogenic carcinoma. The frequency with which the disease is detected at autopsy depends upon the age of the patients examined.[2] Not only is this disease being more frequently detected, but also the incidence is increasing, owing both to a generally aging population and to the greater life expectancy of individuals with chronic illnesses which predispose to thromboembolic disease. The anaesthetist will be called upon to provide anaesthesia for these patients, involving various surgical procedures. The relatively high incidence of pulmonary embolism as a cause of death in the postoperative patient becomes apparent from an analysis of Table I.

TABLE I

RESULTS: INCIDENCE OF AUTOPSY-PROVEN DEATHS DUE TO PULMONARY EMBOLISM (July 1, 1955–June 30, 1959)

Anaesthetics		90,710	
Deaths		105	
Mortality rate		1: 864	
Age			
Years	1–29	30–59	60–89
Nos.	2	32	71

Pathogenesis and Pathology of Pulmonary Embolism

(*a*) *Embolic material.* Under certain circumstances foreign materials such as air, fat (3 patients), amniotic fluid, bone, neoplasm (1 patient), or extraneous

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objects (bullets) may embolize to the lungs. The most common and clinically the most important foreign material is an intravascular blood clot (101 patients).

(*b*) *Sites of venous thrombi.* The usual sites of venous thrombi which detach and embolize to the lung are the veins of the lower extremities (94 patients), the chambers of the right heart (4 patients), and the pelvic veins (7 patients). The majority of reports indicate that well over half of fatal pulmonary emboli originate in the leg veins.

(*c*) *Predisposing factors.* Thrombosis of veins is related to three basic predisposing factors: venous stasis, injury to blood vessel wall, and physicochemical alterations in the blood constituents.[3,4,5]

Conditions which cause stasis of blood in veins predispose to the formation of thrombi. One of the most common conditions is cardiac decompensation due to heart disease of all types (20 patients). Thrombi occur in veins of the lower extremities during the course of many chronic illnesses, particularly those associated with debility and requiring prolonged bed rest (26 patients). Pulmonary embolism is seen in patients with pulmonary emphysema[6] (8 patients). It occurs during pregnancy (1 patient). In this series it occurred most commonly following abdominal and pelvic operations (Table II [51 patients]). Twelve patients (11.4 per cent) had fractured femurs. Only three cardiovascular surgical procedures were involved. Does the anaesthetic state or technique contribute to stasis and thus predispose to pulmonary embolism? Sixty-seven per cent of the patients had general anaesthesia and 30.4 per cent had spinal anaesthesia. More will be said of this aspect in the discussion to follow.

TABLE II

RESULTS: PREDISPOSING (?) FACTORS IN AUTOPSY-PROVEN PULMONARY EMBOLISM

Operation	
Abdominal	27
Pelvic	24
Fractured femur	12
C.V.S.	3
Anaesthesia	
General	71
Regional	34
Hypotensive episode	27
Special techniques	19

Injury to blood vessel walls in the lower extremities may be complicated by the development of thrombophlebitis or phlebothrombosis of leg veins. Intravenous administration of fluids into leg veins may predispose to phlebothrombosis and to subsequent pulmonary emboli (8 patients or 7.6 per cent of the fatal cases). Thrombi may form within the right atrium or atrial appendage in those diseases which result in enlargement of the right atrium or atrial appendage (2 patients) and in atrial fibrillation (11 patients). Previous subendocardial injury of the right ventricle, as occurs in myocardial infarction (13 patients), may lead to the formation of mural thrombi which may subsequently detach and embolize to the lungs. Thrombosis of the pelvic veins results most often from infections

or tumours of the bladder, prostate (20 patients), rectum, uterus, or fallopian tubes.

Physicochemical changes in the blood constituents predispose to venous thrombi (3 patients, one each with anaemia, thrombocytosis, and polycythemia rubra vera).

(*d*) *Sequelae.* Trauma to small vessels is followed within 15 to 30 seconds by a localized vasoconstriction.[7,8] Next, an agglutination of platelets occurs. This agglutination and subsequent lysis of the platelets is followed by the liberation of serotonin (5-hydroxytryptamine). Serotonin is a powerful vasoconstrictor for vessels both intact and injured, local and distant. This vasoconstriction may occur for as long as 30 min. Following the vasoconstriction the fibrin clot is formed within a few minutes. Because injected serotonin produces a rise in venous, right atrial, and pulmonary artery pressure, with a fall in systemic blood pressure,[9] probably by the mechanism of pulmonary vasoconstriction, Smith and Smith[10] have implicated serotonin release from blood clot and infarcted lung as a factor in the production of the systemic effects of pulmonary embolism. Sequelae which result from a pulmonary embolus are often unpredictable, differ in separate individuals, and vary according to the size and location of the embolus, the pre-existing state of the pulmonary and cardiovascular systems, the influence of autonomic reflexes, as well as to other poorly understood factors.[11]

Experimental evidence in dogs[12] indicates that an acute obstruction of approximately 70 per cent of the cross-sectional area of the pulmonary circulation is required to lower the pulmonary blood flow sufficiently to decrease systemic blood pressure or to induce right heart failure. Occlusion of more than 80 per cent of the pulmonary vascular bed is necessary to cause death.

(*e*) *Natural history.* The true necrotic infarct heals by fibrosis. Eventually, only a shrunken scar remains at the original site of infarction. Cavitation or sloughing rarely develop. Pulmonary abscess may rarely occur. Large clots, which occlude the pulmonary artery or both main branches, lead to rapid death. An embolus which occludes a major branch of the pulmonary artery or occasionally one which terminates in a lobar branch may prove fatal. Death in this instance is usually attributed to acute pulmonary hypertension resulting from reflex or possibly serotonin-induced pulmonary arterial vasoconstriction. According to Weidner[13] the reflex effect is initiated only in vessels less than 25–100 μ in diameter and is mediated through the sympathetic nervous system.

The normal pulmonary arterial pressure of 16/7 to 30/15 mm. Hg is dependent upon a balance between (i) right ventricular output, (ii) resistance of the pulmonary vascular bed, and (iii) respiratory thoracic pump mechanisms and possibly alterations in resistance to air flow.[14] It is evident that mechanical blockade alone, from massive pulmonary emboli, may alter one or all of these factors markedly, leading to gross alterations in pulmonary blood pressure.

Pathologic-Physiology and Clinical Manifestations

Pulmonary embolization in surgical patients appears more often as a single massive episode and less often with preliminary non-fatal episodes than in

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medical patients. Evidence of thrombophlebitis directing attention to the need for treatment is also less frequent in surgical patients (Table III). Pulmonary embolism was unsuspected in 103 of the 105 patients who died following operation. Some of these patients had serious, uncontrolled disease, and continued on a downhill course following operation. The clinical manifestations, in many instances, were caused by the primary disease. There was no evidence of pulmonary embolism until the terminal episode, except for 7 of the 105 patients studied. Apart from emboli of cardiac origin dislodged at operation, thromboembolic phenomena were rare in the first three days in most series studied.[6] In our study, 31 of the 105 cases occurred within one to seven days but most of these occurred in the latter half of the first postoperative week. Pulmonary embolism tended to occur in the second week (40 patients) or later (23 patients in the second to fourth week), even as late as the fifth week (4 patients), despite early ambulation.[18]

TABLE III

RESULTS: CLINICAL MANIFESTATIONS AND PATHOLOGIC-PHYSIOLOGY OF PULMONARY EMBOLISM

Signs and symptoms	Nos.	Pathologic-physiology
Massive and single	98	
Preliminary non-fatal	7	
Dyspnoea		Hypoxia, autonomic reflexes
Substernal chest pain		Reduction of coronary blood flow
Tachycardia		Reflex
Anxiety, Syncope, Convulsions		Cerebral ischaemia
Abnormal E.C.G.		Right ventricular strain
Shock		Decreased cardiac output
Right side cardiac failure		Mechanical, reflex block of pulmonary circulation
Fever		Tissue necrosis
Sudden death		Decrease in cardiac output, acute pulmonary hypertension

(*a*) *Pulmonary embolism.* The clinical manifestations of pulmonary embolism are protean.[1,11,15] Table III represents these signs and symptoms in approximate order of importance and frequency. Most individuals first develop symptoms related to pulmonary embolism followed by those due to infarction.

(*b*) *Pulmonary infarction.* The salient signs and symptoms of pulmonary infarction are pleuritic chest pain, X-ray densities, fever, hemoptysis, cough, dyspnoea, tachycardia, elevated leukocyte count, and E.S.R.

(*c*) *Suggestive of pulmonary thromboembolism.* The signs and symptoms suggestive of pulmonary thromboembolism were unexplained fever; fever not responding to chemotherapy; increased severity of congestive heart failure, paroxysmal arrhythmia, tachycardia, digitalis toxicity, and mercury fast oedema in patients with congestive heart failure; unexplained "bloody" pleural effusion; lung abscess on X-ray; and unexplained leukocytosis.

(*d*) *Differential Diagnosis.* There are no specific physical signs by which pulmonary infarction can be differentiated from other pulmonary diseases associated with consolidation of the parenchyma.[6] Moreover, the signs and symptoms may

closely simulate other disease processes involving the lungs, heart, abdominal organs, or the central nervous system. Differentiating a pulmonary infarct in the postoperative period from pneumonia, atelectasis, or pleural effusion may be very difficult. Many cases of pulmonary embolism closely resemble myocardial infarction, angina pectoris, or congestive heart failure. Cyanosis is uncommon in myocardial infarction unless cardiac failure supervenes.[16] Recently, Robin[17] has suggested a physiologic approach to the differential diagnosis in a patient with suspected pulmonary embolism by simultaneous measurement of arterial and endtidal carbon-dioxide tensions. In the absence of pulmonary infarction, a difference of less than 5 mm. Hg implied either no embolism or an embolus occluding less than the equivalent of a lobar branch of the pulmonary artery. In the absence of emphysema, a large difference indicated pulmonary vascular occlusion.

Discussion

Pulmonary embolism presents a definite problem to the anaesthetist. This is apparent from the relatively high incidence of death from pulmonary embolism in autopsy-proved, postoperative patients. Many problems remain unsolved. Fundamentally, the mechanism of the thromboembolic phenomenon awaits clarification. Until this is possible, our crude knowledge that the factors of venous stasis, trauma to blood vessel walls, and physicochemical alterations of blood constituents can contribute to thrombopulmonary embolic states must suffice.

Questions arise as to what role, if any, anaesthetic agents and techniques play. Can their known alterations on blood coagulation, cardiac output, systemic arterial blood pressure, pulmonary arterial blood pressure, venous flow, tone and return, predispose to postoperative pulmonary embolism?

It is known[18] that in the postoperative period there is an increase in platelet count and adhesiveness, in fibrinogen, and in prothrombin activity. The peak figures coincide with the time of maximum incidence of thrombosis. Sharnoff[19] has suggested that a stressful situation such as anaesthesia and/or surgery produces hypercoagulability through the following mechanism. There is a disintegration of an increased number of megakaryocytes in the lung capillaries. This produces a sudden, marked increase in circulating platelets and hence a transient blood hypercoagulability, setting the stage for such a thromboembolic complication as pulmonary embolism.

Gernsmyer and co-workers[20] measured brachial and pulmonary artery pressures simultaneously in fifteen healthy persons during consciousness, phenothiazine sleep, and barbiturate anaesthesia. The influence of adrenaline, effortil, noradrenaline, acetylcholine, histamine, tetrazole, pressure upon the eyes, and release of pressure upon the carotid sinus were examined. The behaviour of arterial pressures during change of posture and withdrawal of blood and following infusion of Ringer's solution were observed. Contrary to brachial artery pressures, only minor changes of pulmonary artery pressures occurred due to these drugs and manœuvres. Changes in blood volume caused pressure differences of the same magnitude in both arterial systems.

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Should spinal anaesthesia be indicated or contra-indicated in these patients? Thirty-four of the 105 patients (30.4 per cent) in our series received spinal or peridural anaesthesia. Is intermittent positive pressure ventilation deleterious, especially in the presence of a reduced blood volume? This is implied by the experimental work of Gerst and co-workers.[21] They studied the effects of haemorrhage on pulmonary circulation in dogs and demonstrated that with intermittent positive pressure ventilation, reduction of pulmonary blood flow may lead to complete closure of portions of the pulmonary bed. Following restoration of blood flow, there was some delay before these vessels again reopened. Could this phenomenon predispose to primary pulmonary artery thrombosis or set the stage for pulmonary infarction in the thromboembolic prone patient?

How significant are brief periods of hypotension, arrhythmia, hypoxia, and hypercarbia as precipitating factors in thromboembolism? Twenty-seven of the 105 patients (25.7 per cent) had one or more episodes of significant hypotension during anaesthesia. Eleven had atrial fibrillation and 13 previous myocardial infarctions.

Most of these questions are at present not objectively answerable directly from this review or from a perusal of the sparse prevailing relevant literature. Certainly theoretical consideration and indirect evidence indicate caution and a need for awareness of the factors and problems of the embolic-prone individual. The need for expert anaesthesia and the avoidance of any possible precipitating factor is clearly defined.

Certain facts *can* be concluded.

Conclusions: Factors Influencing the Conduct of Anaesthesia

Since each episode of pulmonary embolism exposes the individual to a mortality risk and some patients with massive or repeated pulmonary emboli die in spite of treatment, the ultimate control of the disease will require its prevention. For this purpose there is need for more accurate means of predicting those individuals who will develop venous thrombi and subsequent embolization, and a method to prevent their formation in the postoperative period. The present means for predicting susceptible individuals are crude, for all patients with known predisposing diseases must be suspected as candidates for pulmonary embolism.

TABLE IV

Conclusions: Pre-Anaesthetic Considerations

(1) Predisposing states
(2) Phlebothrombosis
(3) Pre-Anaesthetic sedation

Pre-anaesthetic Considerations (Table IV)

(a) ***Prevention of pulmonary embolism before operation.***

(1) Attend to medical and surgical predisposing states. This is well exemplified in a recent series involving elderly patients with fractured hips.[22] One hundred

and fifty patients were given phenendione soon after admission and always prior to operation; 150 were not (control series). Pulmonary embolism occurred in no patient under the current influence of the anticoagulant; but in the control series, embolism developed in 18 per cent of cases and fatal embolism developed in 10 per cent of the patients.

(2) Look for already existing thrombosis in the lower limbs. Thrombophlebitis, when fully developed, can be easily recognized by the classical signs of pain, heat, redness, calf tenderness, and distention of superficial veins. One of the early signs of the disease is an increased size of the leg, detected by measurement of the circumference of the calf area. Awareness of the physical signs of incipient thrombophlebitis and a high index of suspicion toward pulmonary embolism will allow the anaesthetist to suspect tentatively many more patients with these conditions.

(3) Adequate pre-anaesthetic medication to remove anxiety and fear, since these factors predispose and have been found to increase coagulability in blood.[18]

TABLE V

CONCLUSIONS: ANAESTHETIC CONSIDERATIONS

(1) Normotension
(2) Cardiac Arrhythmias
(3) Posture
(4) No I.V. into lower limb veins
(5) Venous flow rate

Anaesthetic Considerations (*Table V*)

(1) Rapid, quiet induction.

(2) Adequate oxygenation and removal of carbon dioxide, patent airway, high flow oxygen.

(3) Avoidance of exertion, straining, or "bucking."

(4) Maintenance of normotension, since 27 of the 105 patients reviewed had one or more episodes of hypotension.

(5) Maintenance of normovolaemia.

(6) Non-toxic anaesthetic agents not irritable to myocardium.

(7) Control of cardiac arrhythmias and cardiac decompensation.

(8) ECG available.

(9) Care in posturing, pressure points on veins, avoidance of unnecessary pressure on veins of the lower extremities.

(10) A major cause of intimal damage is eliminated by avoiding intravenous administration of fluids in lower limb veins. Eight of the 105 patients (7.6 per cent) had received intravenous fluids into leg veins. In each instance, autopsy-proven thrombophlebitis and phlebothrombosis occurred and was the most likely source of the fatal pulmonary embolus. However, when this location is absolutely necessary, the routine use of 10 mg. of heparin sodium in each litre of fluid administered is of definite value in minimizing superficial and deep venous thrombosis.[23]

(11) Use of elastic stockings, pressure inflated suits, or elasto-crêpe bandages

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on the lower extremities in order to increase the rate of flow through the veins by decreasing their calibre. Wilkins and Stanton[24] have observed a significant reduction in the occurrence of pulmonary embolism in medical patients by this latter method. They point out that it is important that the stockings fit snugly and be maintained in the proper position. If allowed to wrinkle and to slip downward, they will obstruct rather than augment venous blood flow. McLachlin and McLachlin[25] have used electrical stimulation to maintain calf vein flow during surgery in the curarized patient, since they had demonstrated by cineradiography stasis in calf veins during inactivity.

(12) Rapid, quiet emergence.

TABLE VI

CONCLUSIONS: POST-ANAESTHETIC CONSIDERATIONS

(1) Mobilization
(2) Hydration
(3) Anticoagulants
(4) Venous ligation

Post-Anaesthetic Considerations (*Table VI*)

(*a*) *Prevention after operation.*

(1) Early mobilization of lower extremities. The value of early ambulation is not proven, for in some studies the incidence of pulmonary embolism is unchanged.[26]

(2) Avoid dehydration.

(3) Anticoagulants (chiefly heparin and dicumarol) indicated[18] prophylactically in patients with (i) existing thrombophlebitis or phlebothrombosis of the leg veins; (ii) clinically diagnosed non-fatal pulmonary embolism; (iii) when immobilization is inevitable; (iv) congestive heart failure in emergency operations; (v) past history of thromboembolism; (vi) family history of thromboembolism.

(4) Surgical ligation of the vena cava, or less often of the femoral vein, has been widely employed to prevent pulmonary embolism in patients with thrombophlebitis of the leg veins or to prevent additional emboli in patients with non-fatal pulmonary embolism. Specific indications are:[6] (i) when thrombi in the leg veins continue to cause pulmonary embolism in spite of properly regulated anticoagulant therapy; (ii) when anticoagulants are contra-indicated by the risk of bleeding, chiefly from lesions of the central nervous system, gastrointestinal tract, or post-transurethral prostate resection; (iii) when the patient cannot or will not co-operate with prolonged management of the anticoagulant regimen.

(*b*) *Treatment of pulmonary embolism.* Prompt and adequate supportive measures may be life saving for the patient with an acute pulmonary embolus.

(1) Oxygen to prevent hypoxia.

(2) Vasopressor drugs, to combat shock.

(3) Opiate, to relieve pain and apprehension.

(4) Correct underlying disease.

(5) Supportive therapy, (i) atropine; (ii) serotonin antagonists?

(6) Heparin given initially and continued until hypoprothrombinaemia is induced by one of the coumarin drugs reaches the optimum range. Maintenance of

prothrombin level in the therapeutic range should be continued for several weeks after full ambulation is achieved and all evidence of thrombophlebitis has subsided. In some cases, particularly those with mutiple pulmonary emboli, pulmonary hypertension, and cor pulmonale, anticoagulants should be given for the remainder of the patient's life. Lifelong treatment is also required for patients with rheumatic heart disease who develop atrial thrombi and have multiple attacks of pulmonary embolism.[6]

(7) Surgical ligation of the femoral veins or vena cava, and occasionally pulmonary artery embolectomy.

Summary

The relatively high incidence in a general hospital of autopsy-proven pulmonary embolism as a cause of death in the postoperative patient has been noted. A brief description of some of the main physiologic-pathologic factors involved in the pathogenesis and pathology of pulmonary embolism, with particular emphasis on their clinical implications especially where they pertain to the field of anaesthesia, has been given. Some of the problems which may confront the anaesthetist in dealing with patients prone to develop this condition have been outlined. Factors influencing the conduct of anaesthesia are discussed.

Résumé

Les auteurs ont étudié 105 cas d'embolie pulmonaire, prouvée à l'autopsie, survenus à l'Hôpital Général de Vancouver durant les quatre années s'écoulant du 1er juillet 1955 au 30 juin 1959. Chez 103 des 105 malades, l'embolie a été méconnue. On ne peut obtenir la preuve d'une embolie pulmonaire qu'à l'autopsie.

Dans les poumons, l'embolus peut être de l'air, de la graisse, du liquide amniotique, de la moëlle osseuse, des débris de néoplasme ou des objets de l'extérieur comme des balles. Cependant, ce que nous trouvons plus fréquemment et qui, du point de vue clinique, prend le plus d'importance comme embolus: ce sont les caillots (101 malades dans cette série). Les sites habituels des thrombi veineux qui se dirigent vers les poumons sont les veines des extrémités inférieures, les cavités droites du coeur et les veines du bassin.

Les facteurs prédisposant à la thrombose et à l'embolie pulmonaire sont (1) la stase veineuse, (2) la blessure des parois vasculaires et (3) les modifications physico-chimiques des constituants du sang.

Il n'existe pas de signes physiques spécifiques qui nous permettent de différencier un infarctus pulmonaire des autres maladies qui entraînent la consolidation du parenchyme. Après une opération, un infarctus pulmonaire peut devenir impossible à différencier d'une pneumonie, d'une atélectasie, d'un épanchement pleural, d'un infarctus du myocarde, d'une angine de poitrine ou d'une congestion par défaillance cardiaque.

Alors, la question se pose, quelle est la part de responsabilité, s'il en existe, qui revient aux agents et aux techniques anesthésiques? L'on sait, qu'au cours des suites opératoires, il survient une augmentation de la viscosité et du nombre des plaquettes et une plus grande activité du fibrinogène et de la prothrombine. On a

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émis l'opinion (19) que cela était une réponse à l'agression que causaient l'anesthésie et la chirurgie.

On est d'avis que la fréquence de l'embolie pulmonaire post-opératoire peut être modifiée selon l'attention que l'on porte aux facteurs qui peuvent engendrer des thromboses intravasculaires. Il faut examiner le malade pour dépister précocement les signes de thrombophlébite. Des traitements aux anticoagulants peuvent être indiqués. Au cours de l'anesthésie, il faut insister pour que l'induction soit rapide, douce, que la ventilation soit toujours adéquate, que le volume sanguin et la tension artérielle soient maintenus, qu'on ne fasse usage que des agents les moins toxiques, qu'on dépiste et qu'on traite précocement les arythmies et les décompensations cardiaques et, enfin, qu'on surveille la position sur la table. S'il est possible de la faire, éviter d'administrer les fluides intraveineux dans les veines des membres inférieurs et éviter toute compression sur les veines.

Au cours des suites opératoires, la prévention des embolies peut se faire en faisant la mobilisation précoce des extrémités, un hydratation adéquate et un usage judicieux des anticoagulants. Il peut devenir nécessaire de pratiquer la ligature chirurgicale de la veine cave ou de la veine fémorale.

Lorsque l'embolie pulmonaire est survenue, il devient salutaire de prendre des mesures adéquates de traitement et, cela, promptement. Ce traitement doit inclure d'abord l'usage de l'oxygène pour prévenir l'hypoxie, des vasporesseurs pour lutter contre le choc, des sédatifs pour traiter la douleur et toute autre médication de support. Ensuite, il faut songer au traitement des causes de l'embolie.

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THE ANTISIALOGOGUE EFFECT OF TRIMETHOBENZAMIDE HCL (TIGAN®), TRIMEPRAZINE TARTRATE (PANECTYL®), DIPHENHYDRAMINE HCL (BENADRYL®), DIMENHYDRINATE (GRAVOL®, DRAMAMINE®), AND CYCLIZINE LACTATE (MARZINE®, MARAZINE®)*

ALLEN B. DOBKIN,† and V. GUY CRISWICK‡

IT IS DIFFICULT to tell clinically whether an ancillary drug, which is useful in association with anaesthesia, has useful physiological effects other than those of its primary action unless they are studied specifically. The antisialogogue effects of the following drugs which are used primarily as antihistaminics and anti-emetics are reported here.

Trimethobenzamide HCL (*Tigan®*) is a substituted benzamide which contains the active substance 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)-benzylamine HCL. It is a white, odourless, crystalline powder which is water soluble (more than 50 per cent at 25° C), and has a bitter taste. It has been used primarily as an anti-emetic.[1] Its anti-emetic effect appears to act at the chemoreceptor trigger zone, as with the phenothiazine derivatives, although its chemical structure resembles the dimethyl aminoethoxy antihistamines, such as diphenhydramine. It is not as effective in preventing vomiting caused by strong reflex visceral impulses. It does not cause any hypnotic sedation or behavioural depression as is observed with chlorpromazine. Tigan does not have the antihistaminic or antiadrenaline effects of the phenothiazines or structurally related compounds.[2]

Trimeprazine tartrate (*Panectyl®*) is a phenothiazine derivative whose antihistaminic and anti-emetic properties exceed those of promethazine. It has only a weak antiadrenaline effect, but its spasmolytic effect exceeds that of chlorpromazine. The hypnotic sedative action is of the same order as promethazine. It has been used in the treatment of a variety of allergic disorders to relieve itching, and as a premedicant for children.[3,4,5]

Diphenhydramine HCL (*Benadryl®*) is a benzhydryl derivative which has potent antihistaminic and antispasmodic properties. The other main action of this drug is a marked hypnotic-sedative effect which lasts several hours. An atropine-like action which inhibits sweating and dries secretions is often observed, and is useful in the control of the symptoms of Parkinson's disease.[6]

Dimenhydrinate (*Gravol®*, *Dramamine®*) is a benzhydryl derivative which exhibits some antihistamine properties, but is employed chiefly in the prevention and treatment of motion sickness, irradiation sickness, and post-anaesthetic

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nausea and vomiting. It has been used with only fair results in the treatment of nausea and vomiting of pregnancy. The mechanism of the antiemetic action of this drug has not been elucidated. Drowsiness is the principal side effect.[7]

Cyclizine lactate (*Marzine®*, *Marazine®*) is N-benzhydryl-N-methyl piperazine. This substance exerts both antihistaminic and anticholinergic actions. The antihistaminic action is equal to that of diphenhydramine. Its anticholinergic activity (as measured by its ability to block the blood pressure reducing effect of vagal stimulation) is about 5 per cent of the potency of atropine. Its spasmolytic effect on the gut, however, is less than one per cent when compared to atropine. Its hypnotic sedative effect is less than that of diphenhydramine.[8]

Method

Serial tests were done on eight healthy adult male subjects (ages 20–30 years) using a technique that was reported previously.[9,10,11,12] Each subject had at least twelve tests. Duplicate tests were done with carbaminoyl-choline chloride and adrenaline mixture (control) and the five drugs described above.

The intravenous dose of each drug was selected within the therapeutic range of their optimum antihistaminic or antiemetic effect.

In the control test, saliva was collected for 10 min. before any drug was administered, and then for 30 min. after the intravenous injection of the mixture. In the remaining tests, each drug was injected intravenously at the beginning of the experiment, and saliva was collected for 10 min. Then the mixture was injected, and saliva was collected for a further 30 min. The same parotid gland as was initially selected in each subject was used throughout the series of tests, and volumes of saliva were recorded at 10 minute intervals.

Results

A summary of the data is shown in Figure 1. The mean volume of saliva collected during the 10 min. immediately following the injection of the carbaminoylcholine-adrenaline mixture was taken as 100 per cent. All other measured volumes were then tabulated on this percentage basis. Standard deviations were calculated from the mean volumes of salivary secretion collected, and also expressed as a percentage.

Trimethobenzamide exhibited little consistent effect on salivary secretion, and had no evident side effects.

Trimeprazine, diphenhydramine, and dimenhydrinate caused suppression of salivary secretion during the initial 10-min. period and were more than 50 per cent effective in preventing the secretion of saliva in response to the carbaminoylcholine-adrenaline mixture. Trimeprazine and diphenhydramine consistently caused marked drowsiness in every subject. Only slight or moderate drowsiness was caused by dimenhydrinate.

Cyclizine did not suppress salivary secretion during the initial 10 minutes after administration, but it was very effective in suppressing salivation after administration of the stimulant mixture. Drowsiness was observed more often

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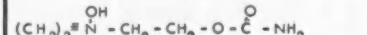
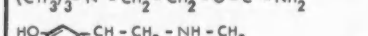
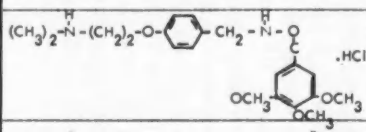
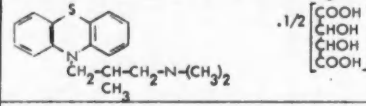
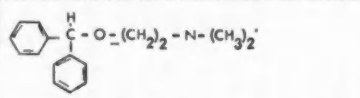
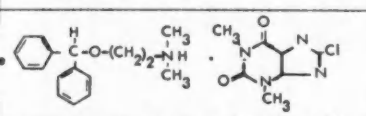
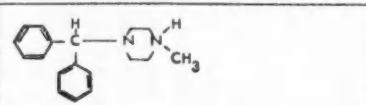
DRUGS	OFFICIAL & CHEMICAL NAME	STRUCTURAL FORMULA	I.V. dose mg.	SECRETION OF SALIVA % OF CONTROL TEST RESPONSE WITH CARBACHOL-ADRENALINE. 10 min. BEFORE	10 min. AFTER	20 min. AFTER	30 min. AFTER	PERCENT REDUCTION of SALIVARY SECRETION
CARBACHOL	Carbaminoylcholine		0.12	2	100*	15	9	-
ADRENALIN (Control)	Epinephrine		0.06	± 2	± 81	± 18	± 7	-
TIGAN	Trimethobenzamide HCl (Roche) N - (p - (2 - dimethylaminoethoxy) benzyl) - 3, 4, 5 - trimethoxybenzamide HCl		200	2 ± 1	78 ± 85	5 ± 5	5 ± 8	Not Significant.
PANECTYL TEMARIL	Trimeprazine tartrate (Poulenc) 10 - (3 - dimethylamino - 2 - methylpropyl) - phenothiazine tartrate		5	1 ± 1	47 ± 35	7 ± 8	5 ± 11	53
BENADRYL	Diphenhydramine HCl (Parke Davis) 2 (benzohydryloxy) - N, N - dimethylethylamine HCl		50	1 ± 1	43 ± 54	4 ± 5	2 ± 3	57
GRAVOL DRAMAMINE	Dimenhydrinate (Homer, Searle) 2 - (benzohydryloxy) - N, N - dimethylethylamine 8 - chlorotheophyllinate		50	1 ± 1	41 ± 48	4 ± 4	2 ± 2	59
MARZINE MAREZINE	Cyclizine lactate (Burroughs Wellcome) diphenylmethyl - 4 - 1 - methylpiperazine lactate		50	2 ± 1	29 ± 28	2 ± 2	2 ± 2	71

* ALL salivary volumes were computed on the basis of this volume = 100.

FIGURE 1

than with dimenhydrinate, but was not as marked as with trimeprazine or diphenhydramine.

Discussion

Trimethobenzamide is suitable only for use as an anti-emetic, as it has no apparent other effects which might be useful as an adjunct to clinical anaesthesia.

Trimeprazine, diphenhydramine, dimenhydrinate, and cyclizine are useful for premedication because they not only have anti-emetic, antihistaminic, and hypnotic sedative properties, but are also effective in partially inhibiting salivary secretions. Since their antisialogogue activity is significantly less than the belladonna derivatives, it is advisable to include one of the latter when one of the above drugs is used for a pre-anaesthetic medicant.

Summary and Conclusions

The effect of intravenous trimethobenzamide, trimeprazine, diphenhydramine, dimenhydrinate, and cyclizine on salivary secretion was studied in eight healthy male adult subjects. A mixture of carbaminoylcholine chloride was used to stimulate secretions. The dose selected for each drug was that used for an optimum therapeutic activity of its most desirable effect.

Cyclizine was the most effective antisialogogue of this group, and it also caused moderate drowsiness. Trimeprazine, diphenhydramine, and dimenhydrinate exceeded 50 per cent effectiveness as antisialogogues, and caused varying degrees of drowsiness.

Trimethobenzamide was not effective as an antisialogogue, and did not cause any other objective effects.

Résumé

Nous avons pratiqué, en duplicata, des tests en série sur huit adultes mâles en santé avec un mélange de chlorure de carbaminoylcholine et d'adrénaline (comme contrôle) puis avec de la trimethobenzamide, de la triméprazine, de la diphenhydramine, du dimenhydrinate et de la cyclizine pour évaluer leur pouvoir antisialagogue. Au cours du test de contrôle, la salive était prélevée du canal de la parotide durant 10 minutes avant l'administration de tout médicament et, ensuite, durant 30 minutes après l'injection du mélange. Au cours des autres tests, les médicaments étaient administrés par voie intraveineuse au début de l'expérience et la salive était ramassée durant 10 minutes. Alors, nous injections le mélange et, de nouveau, nous prélevions la salive durant 30 minutes. Nous avons employé, chez tous les sujets, la même glande parotide que nous avions choisie au début au cours de tous les tests et nous avons tenu compte des volumes à toutes les 10 minutes.

La cyclizine, parmi les médicaments mentionnés ci-haut, s'est avérée le plus efficace antisialagogue et elle a aussi causé des vertiges. La triméthobenzamide a peu ou pas de pouvoir antisialagogue. La trimeprazine, la diphenhydramine et le dimenhydrinate ont dépassé un pouvoir de 50% comme antilialogogues et ils ont causé divers degrés de vertiges.

FIGURE 1

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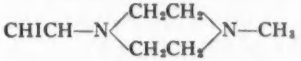
STUDIES OF ANTI-EMETIC DRUGS: A COMPARATIVE STUDY OF CYCLIZINE (MARZINE®), PIPAMAZINE (MORNIDINE®), TRIMETHOBENZAMIDE (TIGAN®), AND HYOSCINE

ELLEN BLATCHFORD, M.B.*

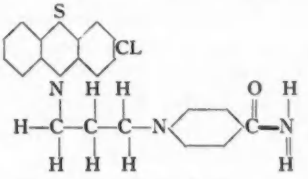
ANYTHING which can alleviate the unpleasant and uncomfortable complication of vomiting during the postoperative period warrants the most arduous and careful investigation. While it would seem that anti-emetic drugs have been covered adequately in the literature of anaesthetic and general medical journals, it was felt that there is always an extra appreciation of their action by first-hand knowledge. In this study we have compared the anti-emetic value of cyclizine lactate (Marzine®), pipamazine (Mornidine®), trimethobenzamide hydrochloride (Tigan®), and hyoscine.

Cyclizine lactate (*Marzine®*) is a white crystaline solid, with the formula

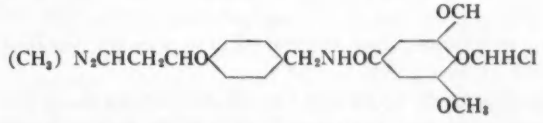


It has both an atropine-like and an antihistaminic action. It depresses the parasympathetic, thus blocking a fall in blood pressure which can result from stimulation of the vagus.

Pipamazine (*Mornidine®*) is a phenothiazine derivative, being a tranquilizer with a separation of the anti-emetic and tranquilizing qualities. Its action is on the medullary chemoreceptor centre. Its formula is:



Trimethobenzamide hydrochloride (*Tigan®*) is a substituted benzamide with the following formula:



Its action is on the "trigger zone" in the medulla without accompanying sedative, toxic, or cardiorespiratory depressant effects.

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Hyoscine is an old and well known drug, and is noted for its cortical depressant action, drying effect, and amnesic properties. Waters in 1938 looked upon hyoscine as a useful cardiovascular antagonist to the effect of morphine, and used it to counteract the depressant effects of pre-anaesthetic sedation.

Investigation

In this series of cases each drug was used for a period of one week, and with the introduction of a control week when no anti-emetic was given, the method of administration formed a five-week cycle. The anti-emetic of the week was ordered with the preoperative sedation (Demerol and atropine), and the anti-emetic was repeated in the recovery room fifteen minutes after arrival. The dosage was as follows:

Cyclizine lactate (Marzine®)
- 50 mg. one hour preoperatively with sedation
- 50 mg. fifteen minutes after arrival in the recovery room

Pipamazine (Mornidine®)
- first series — 5 mg. with preoperative sedation; 5 mg. in the recovery room
- second series — 5 mg. with preoperative sedation; 2.5 mg. in the recovery room

Trimethobenzamide hydrochloride (Tigan®)
- first series — 100 mg. with preoperative sedation; 100 mg. in the recovery room
- second series — 200 mg. with preoperative sedation; 200 mg. in the recovery room

Hyoscine
- gr. 1/100 to 1/200 with preoperative sedation

All the drugs were given intramuscularly.

The patients were observed carefully and any vomiting occurring in the recovery room was charted. Nausea, although noted at the time and recorded, was not considered in the analysis, since it was felt that the positive observation of vomiting was a more reliable factor. All patients were visited on the wards and their reactions during the next twenty-four hours were recorded. A total of 781 patients were observed.

The operative procedures involved in this series of cases ranged from major abdominal work to the usual type of minor operations. In order to test the distribution in each anti-emetic group and in the control group, the operations were classified into major and minor, and the former further subdivided into head and neck, abdominal, and vaginal. There was no significant difference in the distribution (P being .90).

Since it has been noted by Dent *et al.*[1] and Roberts[2] that the type of anaesthetic can be closely associated with postoperative vomiting, it was decided to examine the incidence of volatile anaesthetics and cyclopropane used as against nitrous oxide and thiopentone. The distribution was not statistically significant on comparing the five groups, P being .70, making the groups sufficiently similar

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so that straightforward comparisons could be made with the results observed. It is interesting to note that Belleville, Bross, and Howland[3] found in their investigation that intra-abdominal surgery produced a higher incidence of vomiting. They believe that the experience of the anaesthetist is a factor in producing nausea and vomiting and that light levels of anesthesia produce less vomiting.

It will have been noticed that two series were conducted with pipamazine and with trimethobenzamide. It was found that some very sharp falls in blood pressure occurred in the recovery room when a 5 mg.-dose of pipamazine was administered; consequently, after three weeks observation, it was decided to halve the dose postoperatively to see if this complication could be avoided. In the second series the dose of trimethobenzamide was doubled, since experience and further information indicated that 100 mg. was too little.

Results

TABLE I

A Comparison of the Incidence of Vomiting between Cyclizine and Control Groups

	No vomiting	Vomiting	Total
Controls			
observed value	75.00	68.00	143.00
expected value	87.69	55.31	143.00
	1.836	2.911	4.747
Cyclizine			
observed value	101.00	43.00	144.00
expected value	88.31	55.69	144.00
	1.823	2.892	4.715
	176.00	111.00	287.00
			9.462
	= 9.462 1 d.f.	P = .001	

On comparing the incidence of postoperative vomiting in patients receiving cyclizine with those in the control group, it is seen that cyclizine has a statistically significant effect on the incidence of vomiting (P = .001).

TABLE II

Comparison between Pipamazine and Controls (Combined Series)

	No vomiting	Vomiting	Total
Controls			
observed value	75.00	68.00	143.00
expected value	86.87	56.13	143.00
	1.621	2.510	4.131
Pipamazine			
observed value	103.00	47.00	150.00
expected value	91.13	58.87	150.00
	1.546	2.393	3.939
	178.00	115.00	293.00
			8.070
	= 8.070 1 d.f.	P = .01	

The pipamazine cases were examined in three ways.

(1) The first series of 83 patients receiving the larger dose, P was .05 and just within the bounds of significance.

(2) The second series of 67 patients given the smaller second dose, P was .03, thus indicating slight improvement.

(3) The combined series of 150 patients. An analysis of Table II indicated that pipamazine showed a significant improvement over the control cases (P = .01).

TABLE III

COMPARISON OF THE RESULTS OF TRIMETHOBENZAMIDE ADMINISTRATION WITH CONTROLS (COMBINED SERIES)

	No vomiting	Vomiting	Total
Controls			
observed values	75.00	68.00	143.00
expected values	79.82	63.18	143.00
	0.291	0.368	.659
Trimethobenzamide Hydrochloride			
observed values	112.00	80.00	192.00
expected values	107.18	84.82	192.00
	0.217	0.274	.491
	187.00	148.00	335.00
			1.15
	= 1.15 1 d.f.	P = .30	

The trimethobenzamide group of cases was also studied in three ways (Table III).

(1) The first series, where the patients received 100-mg. doses only, show no improvement on the controls (P = .50).

(2) In the second series in which the dose was doubled, there is no significant improvement (P = .20).

(3) Table III presents the results of the combined cases: 192, consisting of 84 from the first group and 108 from the second series. There is no obvious improvement as P is still too high in value to be significant.

TABLE IV

A COMPARISON OF THE RESULTS PRODUCED BY HYOSCINE ADMINISTRATION WITH PATIENTS IN THE CONTROL GROUP

	No vomiting	Vomiting	Total
Controls			
observed values	75.00	68.00	143.00
expected values	83.86	59.14	143.00
	0.936	1.327	2.263
Hyoscine			
observed values	98.00	54.00	152.00
expected values	89.14	62.86	152.00
	0.881	1.249	2.130
	173.00	122.00	295.00
			4.393
	= 4.393 1 d.f.	P = .05	

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The results of the analysis in Table IV indicate the value of P as .05, which could be accepted as significant.

TABLE V

COMPARISON OF TOTAL SERIES

	No vomiting	Vomiting	Total
Controls			
observed value	75.00	68.00	143.00
expected value	89.54	53.46	143.00
	2.361	3.955	6.316
Cyclizine			
observed value	101.00	43.00	144.00
expected value	90.16	53.84	144.00
	1.303	2.182	3.485
Pipamazine			
observed value	103.00	47.00	150.00
expected value	93.92	56.08	150.00
	1.270	2.126	3.396
Trimethobenzamide			
observed value	112.00	80.00	192.00
expected value	120.22	71.78	192.00
	0.562	0.941	1.503
Hyoscine			
observed value	98.00	54.00	152.00
expected value	95.16	56.84	152.00
	0.085	0.142	.227
	489.00	292.00	781.00
			14.927

= 14.927 4 d.f. P = 0.01

The superiority of cyclizine is still evident in Table V, although pipamazine presents a definite decrease in the number of observed cases vomiting after operation.

DISCUSSION

This study leads one to believe that cyclizine is the most effective anti-emetic of those studied in this series of patients. Chinn and his associates[4] tested this drug for prevention of motion sickness in troops during transport (1952 and 1953), and he felt that it afforded significant protection. Previous experience with cyclizine showed that it had a synergistic effect when combined with a preoperative sedative, and the patients in an earlier series frequently arrived in the operating room too deeply sedated. Therefore, in this study the sedative dose was reduced when combining it with cyclizine. Belleville, Bross, and Holland[5] showed that cyclizine did not increase the post-anaesthetic sleeping time, and that it did not produce significant hypotension. This writer feels that there is a higher incidence of postoperative vomiting in patients who become hypotensive during surgery.

Pipamazine also appeared to diminish the incidence of postoperative vomiting, although its efficiency was somewhat marred by the hypotension which occurred in some patients after the second dose which was given in the recovery room.

There were 14 patients who had a sharp fall in blood pressure in the first series, that is, after the larger second dose, and there were 9 patients with hypotension in the second series. The degree of hypotension varied between 40–70 mm. of Hg, and occurred 10 to 15 min. after the second administration. It was noticed that this complication arose mostly after minor operations, and it was presumed that the interval between the two doses was too short. However, there was one patient who responded unduly to the preoperative administration with a resulting hypotension, and it was considered necessary to postpone the operation because of the fall in blood pressure. It is interesting to notice that the reduction in dosage did not impair its ability to influence the incidence of vomiting favourably.

Trimethobenzamide does not present the same satisfactory picture, and in none of the three series does analysis show statistical significance. Since there were no side effects observed after the administration of trimethobenzamide and it did not appear to potentiate the sedatives given preoperatively, it may be that larger dosage would be more effective.

Hyoscine did show some anti-emetic effect in this study, although the results were not so appreciable as those obtained by Greene and Associates,[6] who, after detailed investigations of a variety of drugs, expressed the opinion that of all drugs tested scopolamine hydrobromide is the drug that most closely fulfills the criteria of the still undiscovered specific anti-emetic.

Summary

The anti-emetic effect of cyclizine (Marzine®), pipamazine (Mornidine®), trimethobenzamide (Tigan®), and hyoscine have been studied and compared in 781 surgical patients selected at random. The drugs were given intramuscularly with the preoperative sedative, and again 15 minutes after arrival in the recovery room. Analysis of the results showed that cyclizine was the most effective in reducing postoperative vomiting, but it was important to realize that it had a potentiating effect on the sedative drugs. Pipamazine also gave statistically significant results, but the incidence of hypotension occurring in the recovery room gave rise to some anxiety. A reduction in dosage minimized this side effect without impairing the anti-emetic effect of pipamazine. Trimethobenzamide did not appear to be effective in this study, and it is thought that since it does not give rise to side effects it could be employed in larger doses, and in this way might prove more effective. Hyoscine given preoperatively gave only fair protection in our series.

Acknowledgments

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Burroughs Wellcome & Co. as Marzine®, trimethobenzamide hydrochloride by Hoffman-LaRoche Ltd. as Tigan®, and pipamazine by G. D. Searle Co. as Mornidine®. We are also indebted to Burroughs Wellcome & Co. for a contribution to the Research Fund. To all, I am most indebted and indeed grateful.

RÉSUMÉ

Chez 781 candidats à la chirurgie, pris au hasard, nous avons étudié et comparé les effets antiémétiques de la cyclizine (Marzine®), de la pipamazine (Mornidine®), de la triméthobenzamide (Tigan®) et de l'hyoscine. Nous avons donné les médicaments par voie intra-musculaire en même temps que la sédation préopératoire et nous en avons répété l'injection quinze minutes après l'arrivée du malade à la salle de réveil. L'étude des résultats nous amène à la conclusion que la cyclizine a le mieux réussi à diminuer les vomissements post-opératoires, mais il est important de retenir qu'elle potentialise les effets sédatifs des médicaments. La pipamazine également a donné certains résultats mais les hypotensions observées dans la salle de réveil nous ont causé des inquiétudes. En diminuant les doses de la pipamazine, son pouvoir antiémétique n'a pas changé, mais ses effets secondaires ont été réduits. La trimethobenzamide, au cours de notre étude, ne s'est pas révélée efficace, mais, étant donné que son emploi n'a donné lieu à aucun effet secondaire, il serait peut-être possible de l'employer à des doses plus fortes et d'obtenir ainsi de meilleurs résultats. L'hyoscine, employée en prémédication, au cours de cette étude, ne nous a fourni qu'une protection ordinaire.

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A NOTE ON THE ANAESTHETIC EFFECT OF SUCCINYLCHOLINE IN CLINICAL SITUATIONS

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SINCE THE NOW CLASSICAL EXPERIMENT of Smith and co-workers,[1] confirmed more recently by Shea and co-workers,[2] it has been universally accepted that the muscle relaxants have no anaesthetic action whatsoever when applied by themselves. This thesis has been further strengthened by lawsuits against anaesthetists by patients who succeeded in convincing juries that they underwent surgery paralysed but not anaesthetized and whose suffering was found to be worth many thousand dollars.

During recent work on various intravenous anaesthetic supplements to nitrous oxide-relaxant anaesthesia, we have encountered somewhat comparable situations in our own practice. Since it is our sincere hope that this series will not increase further and since we believe that these observations are of some general interest, we submit them to our readers at this time.

In the anaesthetic setup where these incidents occurred, the subjects were scheduled for routine abdominal surgery, cholecystectomy, hysterectomy, appendicetomy, and the like. They were premedicated with an oral barbiturate and with intramuscular phenothiazine and scopolamine. Induction of anaesthesia was accomplished by inhalation of a mixture of N_2O 5 L. and O_2 2 L. per minute and the concurrent intravenous administration of increments of some narcotic. Following the disappearance of the eyelid reflex, endotracheal intubation was performed with the aid of suxamethonium, the level of anaesthesia was adjusted by additional increments of the intravenous drugs, and a satisfactory surgical field was maintained by varying the rate of a succinylcholine drip. The pre and postoperative courses of our patients were uniformly favourable from the objective standpoint. Since this series served for the evaluation of intravenous anaesthetics, the patients were questioned in particular detail postoperatively.

To the question, what was the last thing they recalled before going to sleep, two patients replied that they remembered the incision; they did not volunteer this fact earlier in the interview. They described the sensation as comparable to a heavy scratch and they did not recall any feeling of anxiety or distress even on direct questioning. They were able to furnish convincing proof that they were more than partially conscious up to the moment of incision.

A third patient, an intelligent and high-strung woman of 32 years of age, presented a different problem. This lady stated on her arrival in the recovery room and during subsequent interviews that she has been conscious during her abdominal hysterectomy. She was greatly distressed and she required several sessions of "abreaction" and explanation to be semi-placated. She received during a 150-minute intervention the equivalent of 350 mg. meperidine intravenously,

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N_2O 2 L. plus O_2 1 L. per minute with controlled respirations, and 500 mg. of succinylcholine chloride over 100 minutes of the intervention. In describing her experience she fully convinced us that she was indeed conscious for the great part of her operation, yet she complained very little of pain, only of the anxiety caused by being unable to communicate. Immediate review of her anaesthetic chart showed a completely stable pulse and blood-pressure during the intervention. It goes without saying that there was no muscular sign of incomplete anaesthesia once the induction was over, and this in spite of the rather low dose of relaxant employed. Her skin was uniformly dry throughout and her pupils remained constricted during the entire procedure: yet she clearly recalled the anaesthetist lifting her eyelid and looking her in the eye.

Thus far, this would be no more than an exercise in humility by reporting outstanding failures of our anaesthetic efforts were it not for the fact that all three patients were completely oblivious, even after direct questioning, of their intubation. The last patient recalled being extubated and the fact that she could not remember when the tube was inserted into her trachea was the principal argument that helped to convince her that she was unconscious on and off during her operation after all. We are thus confronted with three instances of established consciousness and memory before and very shortly after intubation with complete loss of memory for the intervening period. Since hyperventilation and controlled respiration were established sooner, the only variation that coincided in time with our observation was the intravenous administration of 50 mg. suxamethonium (Brevidil) and the production of transient complete muscle paralysis.

We interpret this observation as confirmation and extension of the work by Shea and others[2] and by Morpurgo and others.[3] It may also furnish an alternative explanation to Gray and Geddes' thesis[4] that hyperventilation potentiates anaesthesia by decreasing the sensory input to the brain. This diminished sensory input might be due to the muscular paralysis necessary for hyperventilation, or at least for the beginning of hyperventilation, not to the decreased pCO_2 caused by hyperventilation or to the mechanical events of the hyperventilation itself. It would also furnish a rationale for the practice of our British colleagues who insist upon complete curarization of their subjects and who prefer to use massive doses of antidotes postoperatively rather than trying to get by on the minimum necessary dose of muscle relaxants.

Summary

Three instances of abdominal surgery are reported where the subjects furnished proof of memory just before and after, but not during, endotracheal intubation. This finding is interpreted as evidence that under clinical conditions muscle relaxants do possess some anaesthetic action.

Résumé

Rapport de trois cas de chirurgie abdominale où les sujets se souviennent des événements précédant et suivant l'intubation endotrachéale, mais non la mani-

pulation elle-même. Ces données indiquent que, employés dans des conditions cliniques, les curarisants possèdent un certain pouvoir anesthésique.

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ANATOMY AND PHYSIOLOGY OF THE NEWBORN RELATED TO ANAESTHESIA

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LIKE ALL RECENT ADVANCES in anaesthesia, the only sound approach to paediatric practice is with an understanding of the basic anatomy and pertaining physiology. From these viewpoints, the child merits separate consideration from the adult. To make the comparison more extreme, it is probably best to think of the newborn baby, because at that age variations from the adult norm will be magnified and more obvious.

Looking at the anatomy of the newborn's respiratory apparatus we find that, unlike the adult whose ribs slope obliquely downwards from the vertebral column, the ribs lie horizontally.[1] This excludes any upswing or bucket handle motion induced by the external intercostals, and so on, and thus there is virtually no costal element in respiration. At the age of one year, the ribs come to acquire the beginnings of obliquity found in adult life, but this change in lie is not completed until the sixth or seventh year. This descent of the ribs is brought about by the rib cage outgrowing the lungs within.

In the newborn the diaphragm lies much lower than in the adult: the right dome reaching T8-9, the left T9-11. This indicates voluminous lung bases, but it must be remembered that respiration is embarrassed because the abdomen is distended by a large liver on the right, and especially after meals by the stomach on the left, while the greater part of the gut is outside the pelvic cavity, which has not yet acquired a capacity proportionate to its size in adult life. Furthermore, shortly after birth the gut begins to contain air and thus increases its volume. Within the chest, the heart and mediastinum, including the rather sizable thymus, take up an undue amount of room. At six months mediastinal structures occupy 43 per cent of the space in the chest while at twelve years the figure is only 33 per cent. This is probably a better indication of lung volume than the cardiothoracic ratio, which in the neonate is normally 0.55, whereas 0.50 is the upper limit for normality in the adult.

The lung is developed by dichotomous branching of the bronchi initially, and in the later stages by irregular branching. This process is found to be proceeding actively in premature babies, but even in the normal full-term infant several further branchings may occur until about twenty-four divisions in all are present. Alveolar development is in various stages of maturity, and many are lined by relatively impermeable cuboidal epithelium.[2]

In the adult the dimensions of the trachea approximate 12 cm. in length and 15 to 20 mm. in diameter. For its size the newborn has relatively greater dead space in its bronchial tree, the trachea measuring 4 cm. in length by 4–6 mm. in diameter.

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From these facts, it would appear that the baby is ill equipped, respiratory-wise, for its separate existence, but from the cardiac viewpoint it can get along more than well enough. Until the moment of birth, the heart has been pumping the blood through the placenta and the body, which adds up to considerably greater work. At birth, by removing the placenta, a large part (25 per cent) of the peripheral resistance has been removed. The proportion of blood between placenta and foetus near term is about 25 per cent placenta, 75 per cent foetus, and if the obstetrician waits for some minutes before clamping the cord it will usually have ceased pulsating and the baby may gain up to 125 ml. of blood.[3] The newborn has about 40 to 50 ml. of blood per pound of weight. The heart has to pump only about 80 per cent of the volume present in intrauterine life through 75 per cent of its previous circulatory bed and much less distance. This reduction in cardiac work is reflected in the fact that the heart diminishes in relative size during the first year of life. The foetal pulse rate of 130 to 180 per min. drops to about 140, an hour after birth, and during the first year, the rate, though variable, averages 110–130. Vagal restraint is minimal. Blood pressure is around 75 to 95 mm. systolic in the first few weeks and bears some relationship to birth weight. Right and left ventricular pressures are similar at birth, but exactly when the adult disparity occurs is uncertain. Cardiac output averages a little over 500 ml. per min. and the stroke volume therefore 4–5 ml. On a weight basis, this cardiac output is roughly twice the adult norm at rest.

Foetal haemoglobin is qualitatively different from the adult type. It has a different oxygen dissociation curve and resists denaturalization by alkalis. At birth there may be 18 gm. Hb of foetal type; at four months of age, all the Hb is of adult character; and at one year of age, 12 gm. Hb per cent is a more likely figure for the healthy child. The significance of foetal Hb is that the oxygen dissociation curve is shifted to the left, which means that it aids the infant by being more readily saturated at low oxygen tensions and while being more acid assists oxygen dissociation. In other words, the baby's blood takes up oxygen more easily and he can make better use of it. Incomplete alveolar development and thick alveolar walls impede gaseous exchange. Carbon dioxide, being more readily diffusible, enters the alveolus more easily than oxygen is taken up. Any newborn child, if observed long enough, will show episodes of periodic breathing. These can be abolished by placing him in an atmosphere rich in oxygen.[4,5] That carbon dioxide plays a relatively unimportant role in effecting respiratory control is generally accepted and, indeed, it is considered that, in the infant, oxygen lack is the fundamental factor in the regulation of breathing.

Most workers agree that the average tidal volume is around 16–20 ml. for a full-term baby, but in prematures it may be much less. During vigorous crying, tidal volumes around 160 ml. have been noted. Respiratory rate is variable, the average probably being around 40 per min. in the first few days, but the normal may range to 100 or more. As a result of the unfinished lung development, the alveolar area available for respiratory exchange is small. The alveolar area per ml. of total lung volume is half that of adult lung, while the respiratory surface per kg. of body weight is about one-third that found in the adult.[6] This requires that one consider what the infant's oxygen needs should be, and here again the

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figures are heavily weighted in favour of the adult. At maturity, oxygen consumption has been established to be around 3.6 ml. per kg., or 266 ml. per min. for a 70-kg. man. In the newborn, the oxygen requirement is around 6–7 ml. per kg. or 21–25 ml. per min. for a 3½-kg. baby. Oxygen requirement is even greater when compared to weight during the age range up to three years. It is also interesting to note that the oxygen needs of the full-term foetus *in utero* is about 1.25 ml. per kg. per min. and 1.5 ml. per kg. immediately it is born, while the figure of 6–7 ml. just mentioned is that of the baby who has become adjusted to his new independent existence. This tremendous increase in oxygen requirement, some 400 per cent, is in all probability largely due to the oxygen needs necessitated by the work of respiration itself. It has been suggested that respiration in the resting adult requires about 10 per cent of the oxygen consumption, but in the baby it is possible that 40 per cent may not be too high an estimate. Finally, considering a 3½-kg. baby and a 70-kg. man, on a weight basis it will be apparent that the baby's tidal volume would be around 500 ml. with a minute volume of some 16,000 ml., roughly twice that of the adult.

In the neonate, dead space is relatively greater than in later life, but to some extent the tracheobronchial tree quickly adapts during growth to overcome this inadequacy. For example, the cross-section of the trachea at birth per unit of lung volume is twice the value of this ratio at the age of one year. On the other hand, the small lumen of the trachea imposes enormous effort on the respiratory musculature. The saggital diameter of the infant's trachea is roughly one-fourth or one-fifth that of the adult. It follows from this, that if the physical laws governing gas flow through the trachea obey Pouiseuille's Law, which states that the volume of fluid flowing through a tube of given length varies as the fourth power of the diameter of the tube, any increase in the rate of gas flow would produce an effect on the resistance to respiration of 4^4 or 256 times that caused by the same increase in flow rate in the adult. The length of the trachea has a less marked effect to benefit the infant. That this physical law has tremendous importance will be obvious to anyone who has seen a child with croup.

I would now like to quote Dr. Ralph Waters, who in 1942 said "in anaesthesia it may be desirable to relieve a weak patient of the energy output necessary to contract the diaphragm and intercostal muscles." I do not think he had children especially in mind when he made this remark, but there can be few aspects of the anaesthetist's practice today where the use of controlled respiration is more generally desirable or more rewarding. Perhaps it should even be the routine method in paediatric work. It requires much greater skill, is exacting in the demands it makes of the anaesthetist, but gives definite advantages to patient and surgeon.

Traditionally, open drop ether has been held to be an excellent method for paediatric anaesthesia, but its drawbacks are many. To begin with, there is the difficulty of inducing and maintaining a reasonable depth of anaesthesia. This is a function of the small tidal volume of the child and the difficulty of vapourizing ether from the mask. The heat necessary for the vapourization of the ether has to come from the anaesthetist's hands and from the atmosphere with the result that it is difficult to prevent condensation of water vapour and ice formation

on the mask, and the child inhales a cold dry mixture of gases. The oxygen tension in this inspired mixture is also somewhat diminished and further reduced at alveolar level where the tension of water vapour is again elevated. The fact that ether at reasonable levels of anaesthesia stimulates respiration reflexly is its greatest safeguard, but this can be very distressing to the surgeon as the overactive diaphragm tends to keep pushing the intestines into the wound. Even at light levels of anaesthesia, hypercarbia is probably present as carbon dioxide elimination with the semi-open mask technique must necessarily be impaired. Good relaxation of the abdomen with this technique can only be obtained by the use of deep levels of anaesthesia associated with respiratory depression and its attendant hazards.

Today, very light levels of general anaesthesia in combination with muscle relaxants and controlled respiration has become the basic method of anaesthesia in most centres for adult patients. I would suggest that with this experience behind us we should now apply it generally in paediatric work where its results are even more rewarding. Due to the immature state of the neuromuscular junction in the baby, reaction to the endotracheal tube is minimal. It can only cause some irregularity of respiration in the neonate who cannot even lift his head off the pillow before he is three months old. Remembering that the larynx is placed rather higher in the neck relative to the cervical vertebrae and that for the first cm. it inclines anteriorly, intubation becomes relatively easy with a little practice. The largest tube that will pass easily should be used and without a wire stilette protruding. With good tubes a stilette should never be required. Stabilization of the tube after insertion with a small saline-moistened pack prevents it slipping out of the larynx and prevents it being shaken about, thus preventing laryngeal trauma. Controlled respiration being the objective, there is a choice of various anaesthetic circuits and systems available. A variety of infant circle systems are available. There is the Water's cannister, the Rees' modification of the Ayre's T-tube, and a choice of unidirectional valves which permit the use of positive pressure respiration. Circle equipment is often only a miniaturized adult outfit and dead space is too great. Three or four ml. increase in dead space is quite significant to a small premature baby whose tidal volume is normally only 5–10 ml. Apart from that, resistance in many circle systems tends to be significant, especially when the directional valves get moist. The Water's cannister is also difficult to construct with elimination of dead space, and it is even more difficult to attach conveniently to a small child. The Rees' system is to all intents and purposes a simple Ayre's T-tube some ten inches long with a small-open ended 500-ml. bag attached distally. Ventilation is carried out by compression of the bag, the end orifice being simultaneously closed with the thumb of the opposite hand. Dead space in this system is the volume of the connection between the side inlet and the endotracheal adaptor and need be no more than one or two ml. A further advantage is its simplicity and the ease with which it can be constructed. Resistance to expiration is minimal, as the system is open to the air. Carbon dioxide elimination is effective provided the rate of gas flow approximates to three times the minute volume, which does not demand excessive flow rates in the young. Unidirectional non-rebreathing valves have

much to offer, but seem to be at a disadvantage at present due to their appreciable dead space and the fact that most are rather clumsy and tend to get badly in the way during surgery, such as that for cleft palate.

The technique of intermittent positive pressure respiration advocated by Rees has been employed by the author in several hundred cases, while its use by the originator and his associates and close followers must amount to many tens of thousands of patients. To date there have been no reports of interstitial emphysema as a major complication. The claim that I.P.P.R. is fraught with the danger of interstitial emphysema is probably unjustified, unless the bronchial anatomy is defective, and then the child may produce the damage spontaneously. Negative and positive pressures of 40–50 cm. of water can easily be produced by the child, and are much more than the anaesthetist would wish to use.[7] These very high intrathoracic pressures are explained by another basic law of physics which says that the pressure difference between the two sides of a spherical membrane in tension is for any given degree of tension inversely proportional to the diameter of the sphere. In the child it is the small diameter of the diaphragm which gives the answer, but it is perhaps worth remembering that it is always desirable to suit the size of the bag on the anaesthetic apparatus to the size of the patient and so to ventilate more effectively with less effort.

As a response to trauma there is, in the neonate as in the adult, a loss of K^+ and N^{++}, but in the adult the K/N ratio is greater than the normal ratio in which these elements exist in normal tissue. This indicates a breakdown of tissue, and additionally a loss of K^+ from tissues where the N^{++} is preserved. In the neonate, on the other hand, the K/N ratio approximates that found in lean muscle, indicating cellular breakdown without extra loss of K^+ from other cells.[8] We know that the infant under three months of age is sensitive to the anti-depolarizing relaxants which depress ionic migration, but he is relatively resistant to the depolarizing drugs like suxamethonium which result in ionic transfer. It is postulated that this variation from the adult type of response may stem from the infant's resistance to intracellular K^+ loss, in response to the hormonal effects of trauma. Alternatively, as in the myasthenic patient, a circulating curariform agent may be responsible.[9,10] This is not altogether impossible in view of the size of the thymus. At any rate, for practical purposes the relaxant of choice where one is needed would appear to be suxamethonium, in most circumstances. Though relatively resistant on the basis of weight to suxamethonium, the total dose should be kept as low as possible. This may cause difficulty, as the total amount of fluid to be given may require the use of fairly concentrated solution with the attendant problem of measuring small doses. As a result of the fact that suxamethonium is destroyed enzymatically and in an exponential fashion, the total dosage needed increases enormously when given intermittently leading to greater likelihood of a dual response with change of end-plate function.

It is well known that during anaesthesia infants tend to become hypothermic. In the very young this carries with it the danger, albeit a small one, of sclerema. But while a small temperature drop may not be deleterious and possibly quite advantageous, it is desirable in cases undergoing prolonged major surgery to

keep a check on the temperature and have the baby lying on a controllable heating pad. This tendency towards a drop in temperature is a function of the child's immature heat-regulating mechanism and his very large relative surface area. Older children, on the other hand, tend to become hyperthermic during the more conventional anaesthetic with spontaneous respiration. This hyperthermia may well have some association with so-called ether convulsions by helping to trigger off an already susceptible central nervous system. The use of controlled respiration, on the other hand, avoids this hazard. With the elimination of the muscular effort of breathing and the associated heat production of muscular contraction, body temperature tends to drop. Advantage has been taken of this fact in the treatment of salicylate poisoning in children, when treatment is directed at the symptom of hyperpnoea.[11] Prolonged curarization and controlled respiration allows the temperature to return to normal levels, and the child is tided over the crisis until excretion has removed a large part of the poison.

During the first few days of life, the infant loses some 10 per cent of body weight. Losses up to 20 per cent occur occasionally and are not usually harmful. Nursing in an atmosphere approaching 100 per cent humidity and preferably about 85° F. halves the estimated insensible fluid loss which becomes roughly 14 ml. per kg. per day. If the child is not initially dehydrated, he can be left without fluids for two or three days. Subsequent to surgery, Rickham recommends only 5 ml. per hour of 1/5 N saline for the first two days (that is, 120 ml. per day) and 10 ml. per hour on subsequent days. These amounts are for full-term infants, and in premature infants the infusion would be reduced. The basic infusion fluid in babies is 1/5 N saline in glucose water, as the kidneys in the very young have difficulty in excreting salt. Potassium loss is minimal and is disregarded, except in the presence of prolonged gastric suction, which, if continued for three days or more, requires the daily administration of 60 ml. of Darrow's solution.[12]

An aspect of postoperative care is the desirability of nursing the patient in the head-up posture if at all possible, laying him on his side and turning him at least three-hourly. Aspiration of vomit is not a problem in the lateral position, and the child's respiration is facilitated. Atelectasis, if it occurs, invariably starts in the poorly-aerated upper lobes and spreads from there. It is worth noting that the bronchi of the upper lobes run almost directly backwards in the infant. The treatment of atelectasis should include hourly percussion with the finger-tips, and nursing with the affected side uppermost. This is often effective, but if it fails suction of the tracheobronchial tree with a fine rubber catheter is often efficacious, especially when the right side is affected. Left-sided involvement not infrequently requires bronchoscopy however, and this may have to be repeated.

Summary

Emphasis is laid on anatomical and physiological differences that exist between the child and the adult, with special regard as to how these variations may influence the anaesthetist in his management of paediatric cases. It is suggested

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that the adoption of a method involving the use of light general anaesthesia, intermittent positive pressure respiration, and, when necessary, muscle relaxants should overcome some of the disadvantages of techniques involving deeper levels of anaesthesia and spontaneous respiration. Differences in the infant's response to the muscle relaxant drugs and suggestions on fluid therapy are briefly indicated.

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Résumé

L'on a démontré que, en comparaison de l'adulte, l'enfant et plus particulièrement le nouveau-né possède une réserve respiratoire considérablement réduite. Cela est dû, d'une part, à une surface relative beaucoup plus petite des alvéoles respiratoires et à leur développement incomplet si on les compare au poids corporel et, d'autre part, à un besoin d'oxygène beaucoup plus grand. Le travail de la respiration, on l'a démontré, est également plus considérable; cela est dû au rythme plus rapide de la respiration, à la résistance au courant d'air à travers une petite trachée et à sa dépendance de la contraction diaphragmatique. Chez le nouveau-né, l'influence essentielle que régit la respiration est plutôt le manque d'oxygène que l'excédent de CO_2. Employer, chez les enfants, les méthodes conventionnelles d'anesthésie, c'est-à-dire la respiration spontanée et ce l'anesthésie profonde requise parfois pour certaines opérations, est une chose condamnable et nous sommes d'avis qu'il serait préférable de soulager l'enfant de l'effort qu'il doit faire pour respirer en employant une technique incluant une respiration à pression positive intermittente, une anesthésie générale légère et, si les circonstances l'exigent, l'usage de myorésolutifs. Chez le nouveau-né, le suxamethonium semble être le médicament de choix. Comme liquide à administrer, un mélange de 1/5 de solution salée et glucosée isotonique semble l'idéal à cause de l'immaturité des reins et de leur difficulté d'excréter le sel. Au cours des deux premiers jours post-opératoires, nous ne conseillons pas de donner plus de 120 ml par jour de ce mélange et, par la suite, 240 ml par jour. On ne porte pas attention au remplacement du potassium, excepté chez les malades qui ont une aspiration gastrique prolongée. On doit nourrir ces malades en leur maintenant la tête élevée et les tourner régulièrement sur un côté et sur l'autre et, de préférence, dans une atmosphère à 85°F. et contenant 100% d'humidité.

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AN ANAESTHETIC RECORD

DOUGLAS A. C. MACDONALD, M.D., C.M.*

ANAESTHETIC RECORDS are many things to different people. To the senior medical student and possibly to the interne they are examples of symbolization: for the clinical instructor and teacher they supply the essential threads of each anaesthetic story, and provide object lessons of pharmacological and physiological events occurring daily in practice; in clinical research they supply answers to questions of probability and possibility; and to our colleagues in other special fields they may be as incomprehensible as our universe. It is only in recent times that precise and accurate records have been considered necessary in anaesthesia, but now they may well point the way toward future anaesthetic horizons.

We may ask, what information should be on the anaesthetic record? What is significant and what is not? The anaesthetic record should show one of the most detailed events in the patient's clinical life. The story should be complete from the first preoperative visit to the last postanaesthetic visit.

To ensure the accuracy and detail required of such a record and to record by hand the minute to minute events, vital signs, and drugs given, it is necessary to resort to the use of abbreviations and symbols. The form of record presented here was evolved for daily use in a small hospital, and is planned to include the most accurate and detailed information with the least possible writing. It contains less detail than the I.B.M. or Keysort anaesthetic records, but still retains sufficient flexibility and detail to permit utilization in any hospital practice.

Consideration of this record may be conveniently divided into two sections: the first recording events from the preoperative visit to the termination of anaesthesia, and the second those from the arrival in the recovery room until the final post-anaesthetic visit. The first of these two parts is illustrated in Figure 1.

Each of the two major sections of the anaesthetic record may be considered as consisting of a number of parts, each useful for the recording of specific data. In Figure 2, the section placed at the head of the chart contains information of a general nature, including the blood group, pre and postoperative diagnosis, operation proposed and operation performed, and the names of the surgeons involved. Much of this information is entered while the chart is being initially assembled.

Figure 3 records the pre-anaesthetic evaluation, and has appropriate areas for recording information gleaned from the chart, and recent laboratory data of interest to the anaesthetist. Features included are the personal anaesthetic history of the patient, what maintenance medication the patient is taking (for example, cortisone), significant recent weight loss (often an indication of subliminal hypovolaemia), and whether the patient has or is suspected of having a full stomach. When the patient has been visited, the operative risk is judged and

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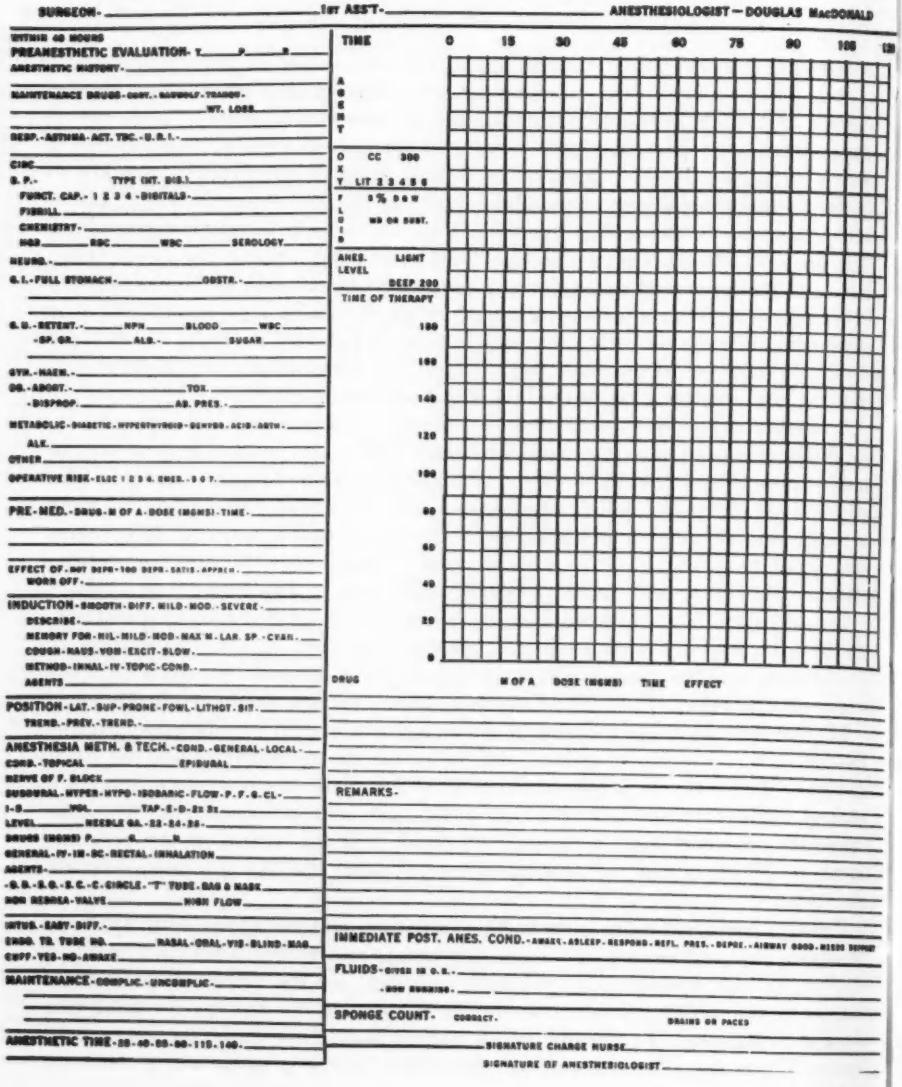

FIGURE 1

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CH'TOWN HOSP. HOSPITAL NO. _____ ROOM _____ DATE _____ M F AGE _____ WEIGHT _____ BLOOD GROUP - A - B - AB - O. RH NEG. POS.

NAME _____ ADDRESS _____

DIAGNOSIS - PRE - _____ OPERATION - PROP. - _____

- POST - _____ - DONE - _____

SURGEON - _____ 1ST ASS'T - _____ ANESTHESIOLOGIST — DOUGLAS MacDONALD

FIGURE 2

WITHIN 48 HOURS

PREANESTHETIC EVALUATION - T _____ P _____ R _____

ANESTHETIC HISTORY - _____

_____

MAINTENANCE DRUGS - CORT. - RAUWOLF - TRANQU. -

_____ WT. LOSS _____

_____

RESP. - ASTHMA - ACT. TBC. - U. R. I. - _____

_____

CIRC. _____

B. P. - TYPE (HT. DIS.) _____

FUNCT. CAP. - 1 2 3 4 - DIGITALS - _____

FIBRILL. _____

CHEMISTRY - _____

HGB _____ RBC _____ WBC _____ SEROLOGY _____

NEURO. - _____

G. I. - FULL STOMACH - _____ OBSTR. - _____

_____

_____

G. U. - RETENT. - _____ NPN _____ BLOOD _____ WBC _____

- SP. GR. _____ ALB. - _____ SUGAR _____

_____

GYN. - HAEM. - _____

OB. - ABORT. - _____ TOX. _____

- DISPROP. _____ AB. PRES. - _____

METABOLIC - DIABETIC - HYPERTHYROID - DEHYDR - ACID - ARTH. - _____

ALK. _____

OTHER _____

OPERATIVE RISK - ELEC 1 2 3 4. EMER. - 5 6 7. _____

_____

PRE - MED. - DRUG - M OF A - DOSE (MGMS) - TIME - _____

_____

_____

_____

EFFECT OF - NOT DEPR - TOO DEPR - SATIS - APPREH. - _____

WORN OFF - _____

FIGURE 3

recorded, and premedication is ordered. It should be noted that here, and wherever practical in this record, the name of the drug, dose in mg., and method and time of administration are recorded. The effect of premedication will be judged and recorded in the pre-anaesthetic interval.

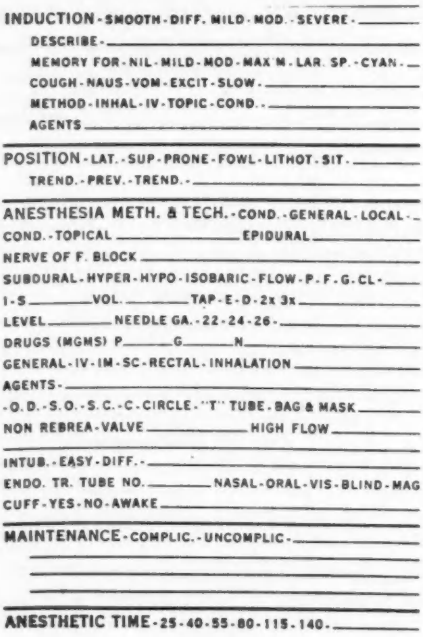
INDUCTION - SMOOTH - DIFF. MILD - MOD. - SEVERE -
DESCRIBE -
MEMORY FOR - NIL - MILD - MOD - MAX M. - LAR. SP. - CYAN. -
COUGH - NAUS - VOM - EXCIT - SLOW -
METHOD - INHAL - IV - TOPIC - COND. -
AGENTS
POSITION - LAT. - SUP - PRONE - FOWL - LITHOT - SIT. -
TREND. - PREV. - TREND. -
ANESTHESIA METH. & TECH. - COND. - GENERAL - LOCAL -
COND. - TOPICAL EPIDURAL
NERVE OF F. BLOCK
SUBDURAL - HYPER - HYPO - ISOBARIC - FLOW - P - F - G - CL -
I - S VOL. TAP - E - D - 2x 3x
LEVEL NEEDLE GA. - 22 - 24 - 26 -
DRUGS (MGMS) P G N
GENERAL - IV - IM - SC - RECTAL - INHALATION
AGENTS -
- O. D. - S. O. - S. C. - C - CIRCLE - "T" TUBE - BAG & MASK
NON REBREA - VALVE HIGH FLOW
INTUB. - EASY - DIFF. -
ENDO. TR. TUBE NO. NASAL - ORAL - VIS - BLIND - MAG
CUFF - YES - NO - AWAKE
MAINTENANCE - COMPLIC. - UNCOMPLIC -
ANESTHETIC TIME - 25 - 40 - 55 - 80 - 115 - 140 -

FIGURE 4

The actual anaesthetic experience is detailed in the section shown in Figure 4. The induction and its progression, the patient's memory for the experience in retrospect, and the method and agents used are described in detail. The position of the patient during induction and maintenance is recorded, and finally the anaesthetic method and technique are detailed. This particular part of the record is difficult to assemble and reduce to a reasonable size, and information in it was limited to local anaesthetic usage. There are three main divisions, with details supplied for conductive and general techniques. When the method is conductive anaesthesia, the appropriate type is encircled. If it is subdural, the baricity, type of flow, interspace, gauge of needle used, ease or difficulty of tap and number of insertions of the needle, and amount and volume of anaesthetic drug, glucose, and vasopressor are all described in detail.

If the method is general, then the mode of administration, agents used, and technique are detailed. Maintenance is described in general terms, specific complications are listed, and the anaesthetic time is expressed in economic terms. Anaesthetic agent, rate of oxygen flow, volume and type of fluid used, anaesthetic level, time of drug therapy, and vital signs are signified in the usual way in relation to time on the graph shown in Figure 5.

Figure 6 is a neat and accurate means of describing specific drug therapy during anaesthesia, and is related to the vital signs through the time of drug therapy in Figure 5. If necessary, this is continued into the section for "remarks." In this section of the chart, the immediate post-anaesthetic condition is recorded

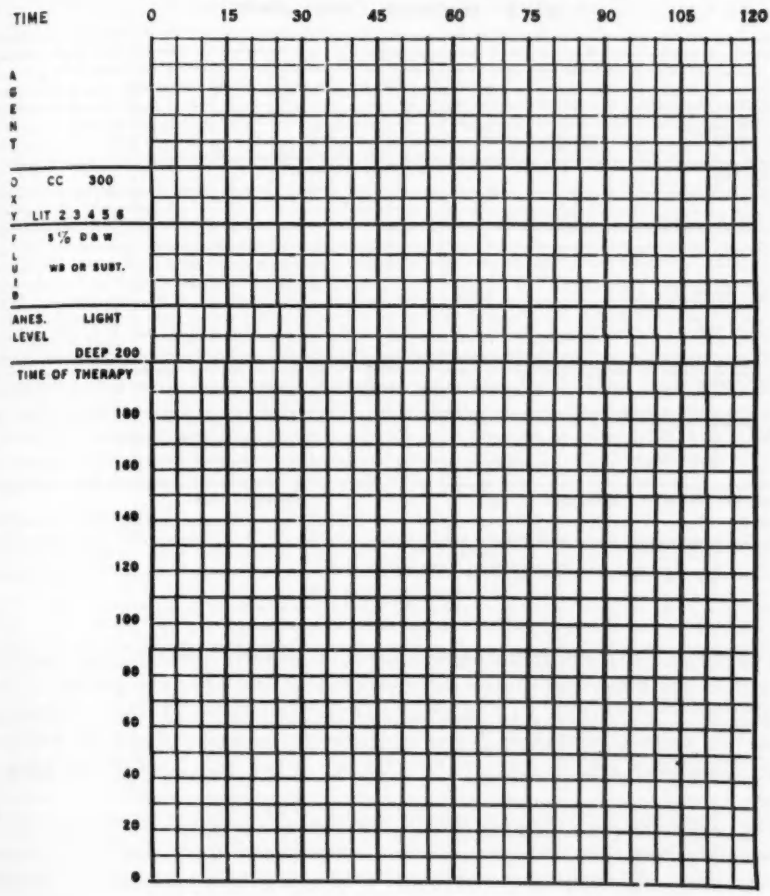

FIGURE 5

and fluids are accurately described in terms of the amount actually given in the operating room and the amount still running when the patient is discharged to the recovery room. Sponge count and the presence of drains or packs are also entered here, and the record is signed by the charge nurse and the anaesthetist.

The second part of the anaesthetic record deals with that period from arrival in the recovery room to the final post-anaesthetic visit. The events of this period are recorded in the form illustrated in Figure 7.

The vital sign chart which is typical for operating room use is available to the recovery room. Space is demarcated for the description of the airway, recording of the temperature, and the presence or absence of pain, restlessness, hypotension, nausea, or vomiting. The state of consciousness and time of awakening after arrival in the recovery room are also recorded.

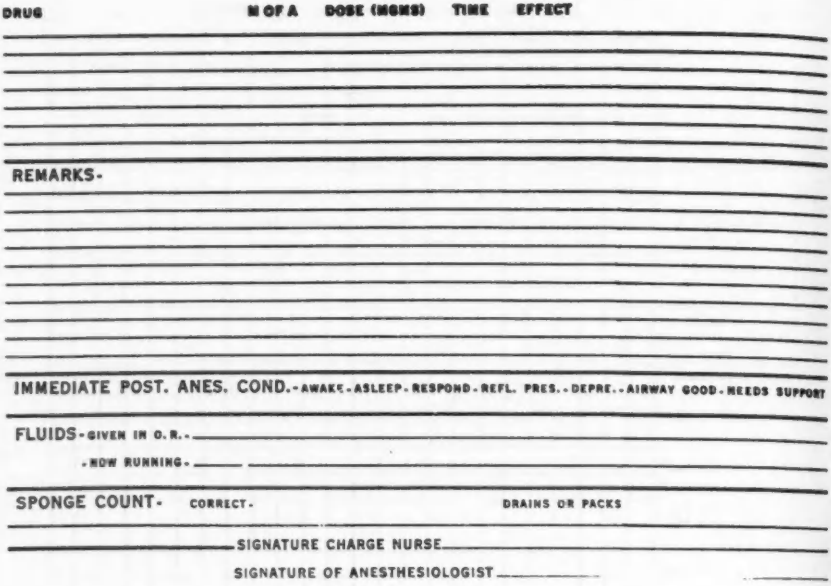

FIGURE 6

The record also includes the description of drugs used with the usual pertinent data, and the total fluid intake and output from the time the patient left the surgical floor until his return. The time of arrival and discharge from the recovery room are entered, and space is provided for any remarks which the recovery room nurse may wish to make for the benefit of her associates on the surgical floor.

The post-anaesthetic course should also be recorded in detail, and this is accomplished by simple checking of the complication in relation to the proper postoperative day column. An adequate area is provided for recording remarks for greater detail.

In order to relate the morbidity recorded during anaesthesia and the post-anaesthetic course to the various methods and techniques, agents and regions, it is necessary to have this information in another area. In our hospital we find this most easily done in the regular operating room record book in a special anaesthetic section. Also recorded is the date, case number, name, age, operation, surgeon, assistant, preoperative and postoperative diagnosis, hospital number, address, responsible party, and information concerning the patient's insurance coverage such as group number.

Figure 8 illustrates the special section in which we record specific anaesthetic information under proper headings. The main subdivisions such as technique, agent, region, risk, complications, and for a pathology specimen are self-explanatory. Most of the subheadings are simply completed by a check mark and these are totalled at the bottom of the page, and carried forward monthly and yearly.

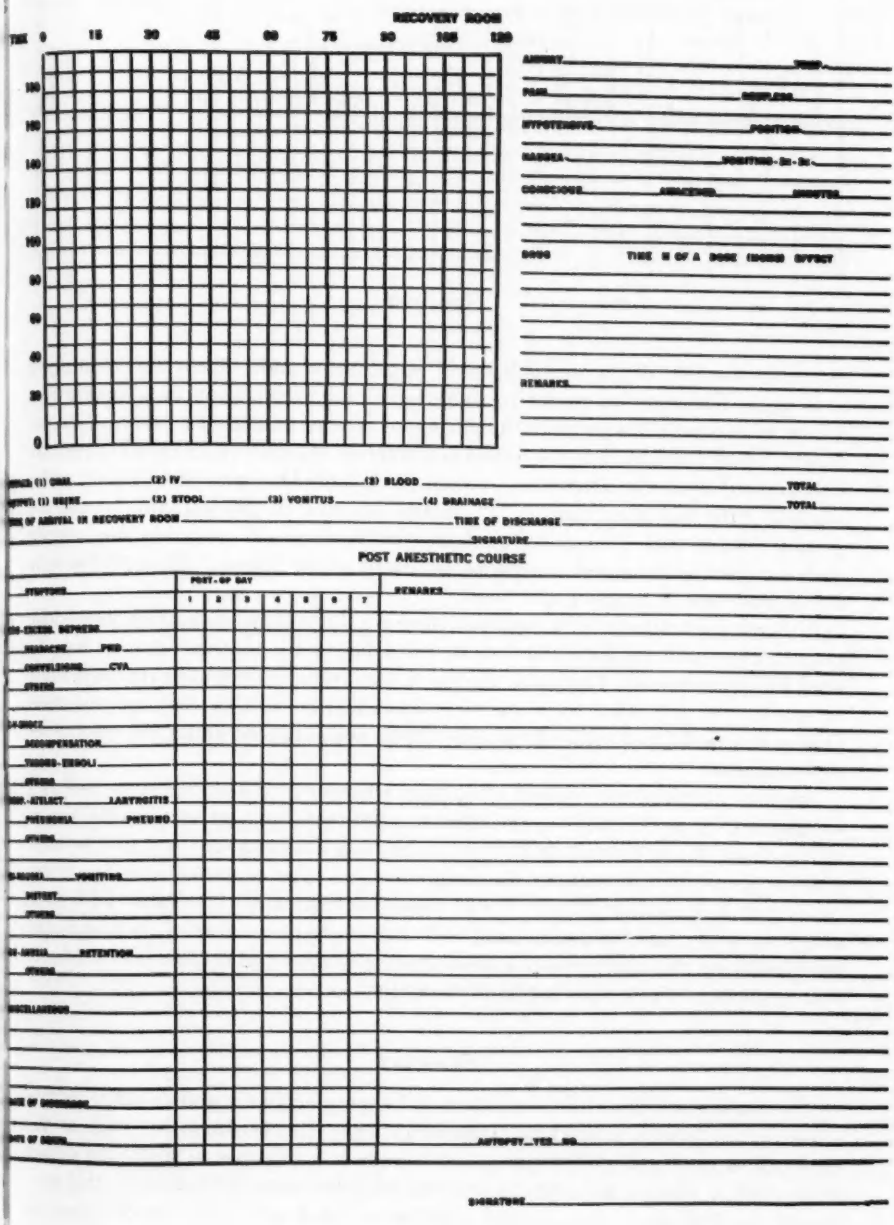
RECOVERY ROOM
TIME 0 15 30 45 60 75 90 105 120
100
90
80
70
60
50
40
30
0
AIRWAY
PULSE
HYPOTENSIVE
NAUSEA
CONSCIOUS
DOSE
REMARKS
POST ANESTHETIC COURSE
POST-OP DAY
1 2 3 4 5 6 7
REMARKS
SIGNATURE

FIGURE 7

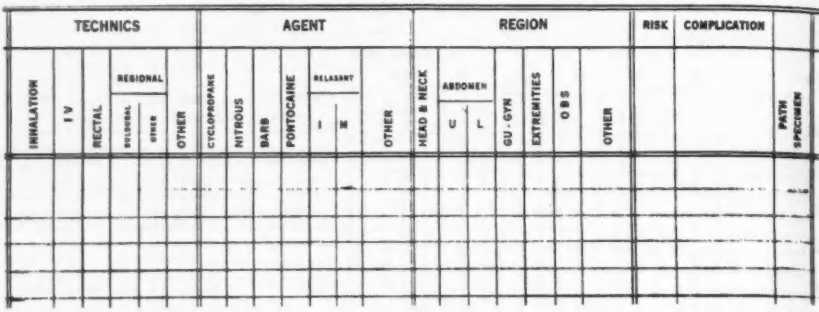

FIGURE 8

However, because of the multiplicity of possibilities under agent and technique, it is again necessary to resort to some form of symbolization or abbreviation. These, of course, will vary with the particular type of anaesthetic practice. Accordingly, under technique in the inhalation column, the particular type is available and marked from the anaesthetic record, such as O.D. (open drop); if an endotracheal tube has been used a "T" is also inserted in this column. Under the section dealing with the agent, symbolization is increased, as rarely used agents such as ether, trilene, and vinethene are listed under "other." Despite the wide use of fluothane it is also listed here.

The relaxant column is a problem, because very often succinylcholine alone may be used only for induction, or, on the other hand, another relaxant may be used for maintenance. Therefore, the particular relaxants are indicated according to whether or not they were used for (I) induction and/or (M) maintenance. Operations performed under local anaesthesia are indicated under the column for other agents.

Another problem is to record accurately whether or not an agent is used as a supplement or as the main agent. This has been resolved by varying the size of of the check mark; a small check mark indicating a supplement and a large mark a main agent. In this manner the frequency and type of use of each agent and technique is recorded. Monthly and yearly statistics are available with little effort for study and for comparison with the morbidity statistics. It is expected that following this approach an anaesthetist may alter and confine his techniques and methods to those with the least morbidity.

SUMMARY

The author has described a method of keeping accurate and detailed records covering the whole anaesthetic experience from the preoperative visit to the final post-anaesthetic visit. From these records it is possible to study the details of morbidity related to anaesthesia, and it is felt that by following this or a similar outline each anaesthetist will be enabled gradually to decrease his morbidity figures.

Résumé

L'auteur décrit une méthode de conserver, de façon précise et détaillée, tous les faits survenant au cours de l'anesthésie depuis la visite préopératoire jusqu'à la dernière visite postopératoire. Avec de semblables dossiers, l'auteur nous assure qu'il est possible d'étudier tous les détails de la morbidité pouvant se relier à l'anesthésie et il a la conviction qu'en adoptant cette méthode ou une semblable, les anesthésistes seraient capables de diminuer progressivement leurs pourcentages de morbidité.

LETTERS TO THE EDITOR

Nuffield Department of Anaesthetics,
Radcliffe Infirmary,
Oxford

SIR:

I wonder whether I may take advantage of the opportunity presented by your publication of the two papers by Professor Robson and his co-authors to make some personal comments on the fascinating subject of mental performance under nitrous oxide.

Professor Robson and his colleagues mention the possible similarity between anaesthesia and head injury or electroshock therapy as regards retrograde amnesia. I think it is important to bear in mind, however, that as far as anaesthetic agents are concerned, there is little evidence that retrograde amnesia occurs. Several cases are known to me in which patients have recalled the experience of being intubated, and in a recent case of my own a patient distinctly remembered hearing me counting aloud during the first minute of trichlorethylene administration after intubation under thiopentone. This case was perhaps particularly interesting in view of the fact that the patient had over four hours of complete amnesia following the termination of the anaesthetic.

The ability to learn non-meaningful syllables is certainly depressed under the influence of nitrous oxide, and we (Parkhouse *et al.*, 1960) were also able to demonstrate that with 40 per cent N_2O delayed recall of presented material (that is, 30 minutes after resumption of air breathing) is relatively more impaired than immediate recall. Surely, though, one need seek no very abstruse explanation for this: in common-sense terms, it is the subject's *concentration* which is interfered with. Before an experiment the subject is alert, attentive, and anxious to do his best, and I believe that this is responsible for much of the apparent facilitation or "fixing" of memory at this stage. Under the influence of nitrous oxide, the subject resembles a sleepy person, a bored person, or an intoxicated person; he no longer cares very much about the quality of his performance, he is ready to seize upon any distraction which presents itself or to fall asleep if left undisturbed. We are far from being able to offer exact explanations for these phenomena, but they are surely global effects upon the brain: to attempt an account of them in terms of selective effects of nitrous oxide upon specific functions is a mistake.

My own experiences of pain tests under nitrous oxide, and the experiences of many of my fellow subjects, lead me to believe that impairment of concentration is also important in the assessment of analgesia. This is discoverable, of course, only with a prolonged, continuous pain stimulus: what then happens is that for most of the time there is no awareness of pain because one is thinking of other things. Occasionally, however, one "comes round" to an acute awareness of the continuing pain, but before one has time to analyse the experience, attention has again wandered.

We noted a marked tendency to perseveration under nitrous oxide, and I think this may be important in two ways. Firstly, coupled with a loss of self-critical inhibition, it could very well explain the repetition of the number 2 instead of 6 by Professor Robson's subject. What I am suggesting is that a fully orientated person might well have thought to himself "I can remember the number which was presented to me before: it was 2, but that was under a different concentration of the gas"; whereas under the influence of nitrous oxide the same subject might quite cheerfully repeat his "2" knowing it to be inappropriate but hoping that it might prove acceptable, or be better than nothing. Secondly, although it may be true that nitrous oxide produces a reduction in the rate of accumulation of new remembered events, this does not necessarily imply a reduction in total thought processes since a great deal of mental activity may be devoted to perseveration and to a heightened attentiveness to trivial events.

This lays open the whole question of time estimation under nitrous oxide. The suggestion of Burns *et al.* that distortions of time estimation are attributable to changes in the rate of accumulation of events leads to a well-known paradox. Suppose, for the sake of argument, that when a subject breathed nitrous oxide accumulation of events occurred at one half the normal rate. The number of mental events customarily associated with the passage of one second would then occupy two seconds of clock time. In a given period of clock time there would, therefore, according to the subject, be a smaller number of seconds: for example, one hour would seem to the subject like half an hour. Parodoxically, this phenomenon is described by Burns *et al.* as an *increase* in time estimate. I am reluctant to accept the hypothesis that a subject breathing nitrous oxide makes some kind of mental estimation of time by comparing the rate of accumulation of new events with an arbitrary normal rate, not only because it underestimates the probable influence of introspection and perseveration, but also because it fails to take account of the wide variations that occur, in every-day life, in the rate of accumulation of new events. I believe that the "sense of time," whatever this may be, is determined not so much by the total number of new events as by the rapidity with which they *appear* to follow each other. In some mental states, including those induced by certain drugs, events may seem to follow each other with kaleidoscopic rapidity, and this leads to the impression of a short but crowded period of time rather than a long and "normally" filled one. In any event, I believe the estimation of 15-second periods to be a poor test, and in our studies we abandoned it early on. The principal difficulty is that almost all the subjects count to themselves in order to form a reasonable estimate and again, under nitrous oxide, it is the subjects' ability to concentrate on their counting which is being tested.

Finally, may I make a remark about Professor Robson's findings in regard to proprioception and dizziness. He and his colleagues express surprise at the apparent mildness of proprioceptive difficulties, particularly in view of the fact that many subjects admitted to feeling dizzy. I think that this is not surprising, and I believe that it brings into sharp focus the most important feature of all the work that has been done in this field. The truth is that all tests which are customarily applied are so crude that they can do no more than pick out *gross* changes

in mental performance. Any fairly experienced person, after an hour or two at a cocktail party, can retain sufficient self-control to appear outwardly normal—even relatively exacting tests can be performed. Yet the person in question may feel quite dizzy, and may be very well aware of the fact that his mental state is far from being as normal as it appears. All that a simple proprioception test is capable of demonstrating is that under the influence of nitrous oxide a subject can, by making an effort, perform a task which normally requires no effort at all. When *sustained* tests are employed, the subject makes the necessary effort to begin with but soon loses his concentration. Perhaps if Burns *et al.* had asked their subjects to sight-read a difficult piece of piano music they would have obtained a more striking result!

J. PARKHOUSE

REFERENCE

PARKHOUSE, J.; HENRIE, JOYCE R.; DUNCAN, GLEN M.; & ROME, HOWARD P. J. Pharmacol. & Exper. Therap. *128*: 44–54 (1960).

Department of Physiology,
McGill University,
Montreal

SIR:

We must first thank you for the opportunity which you have given us of reading the letter from Dr. Parkhouse before its publication.

Dr. Parkhouse has legitimately raised a number of technological questions concerned with our two recent publications. These are dealt with below. Far more important in our opinion is Dr. Parkhouse's attack upon the commonly accepted methods in medical research. He appears offended that one should question the "obvious." "Surely," he says, "one need seek no very abstruse explanation" for the fact that the inhalation of nitrous oxide interferes with the ability to learn non-meaningful syllables: "in common-sense terms, it is the subject's *concentration* which is interfered with." Any attempt to account for these facts, "in terms of selective effects of nitrous oxide upon specific functions is a mistake." It is not always wise to accept explanations based upon subjective experience. For example, one could maintain that the well-known rapid accommodation of perception of light touch was due to distraction of the subject's attention to the maintained stimulus. Before 1920 this interpretation of common knowledge would have seemed common sense. We now know that this accommodation is largely a peripheral phenomenon. Equally we might still believe that there were no communicating channels between arteries and veins had not William Harvey questioned the obvious.

We are thankful to Dr. Parkhouse for bringing to our attention two serious omissions from the texts of our papers. We omitted to mention that none of the subjects of our experiments was aware of the composition of the inspired gases. Moreover, we have not reported that all subjects asked to estimate time were

instructed not to count; in many of our experiments they were asked to add together a pair of single digits to insure that counting was impossible.

We should apologize for confusing Dr. Parkhouse about the estimations of time given by our subjects. We agree with him that, for persons breathing nitrous oxide, "one hour would seem to the subject like half an hour" spent when breathing air. For this reason, when asked to estimate a one-hour period by telling us when he felt that 60 minutes had elapsed, he will estimate a period measuring two hours by clock time. This we refer to as an "increase in time estimate."

It would be commendable for any reader to question facts presented to him which were inconsistent with his own findings. He might also justifiably dispute the interpretation of facts. Dr. Parkhouse, however, criticizes us because we were not content to explain analgesia by saying one has no awareness of pain because one is thinking of other things. We have tried to find out why the inhalation of nitrous oxide makes it possible to think of other things. In our opinion it is frequently worthwhile to question subjective experience. It seems to us that the progress of medical science has been largely dependent upon the willingness of practitioners and scientists to question their common sense.

J. G. Robson
B. Delisle Burns

EXAMINATION RESULTS

THE FOLLOWING CANDIDATES were successful in the 1960 Examinations of the Royal College of Physicians and Surgeons of Canada in the Specialty of Anaesthesia.

EXAMINATION FOR FELLOWSHIP OF THE ROYAL COLLEGE OF PHYSICIANS OF CANADA MODIFIED FOR ANAESTHESIA

MARSHALL, DR. B. M., Toronto, Ont.
MATHESON, DR. D. I., Toronto, Ont.
MATTHEWS, DR. R. L., Toronto, Ont.
SLOAN, Dr. I. A., Toronto, Ont.
WRIGLEY, DR. F. R. H., Montreal, P.Q.

EXAMINATION FOR CERTIFICATION IN ANAESTHESIA

BAK, DR. Z., Toronto, Ont.
BARR, DR. M. N., Saint John, N.B.
BENTHAM, DR. W. H., Scarborough, Ont.
BLAKE-KNOX, DR. P. E. A., Bedford, N.S.
BORG, DR. F. X., Downsview, Ont.
BORIGHT, DR. R. R., Montreal, P.Q.
BOWMAN, Dr. H. C., Rosemere, P.Q.
BOYER, DR. D. E., Peterborough, Ont.
CALDWELL, DR. D. Y., Don Mills, Ont.
CHATTERJEE, DR. K., Ottawa, Ont.
CHORLEY, DR. G. E., Edmonton, Alta.
CLEMENT, DR. G. F., Port Credit, Ont.
COCHRANE, DR. W. H., Edmonton, Alta.
COGGINS, DR. B. H., Don Mills, Ont.
CRAYTHORNE, DR. N. W. B., Montreal, P.Q.
DRYSDALE, DR. A. A. M., Fairview, N.S.
DUGGAN, DR. F. A., Kingston, Ont.
DYCKHOFF, DR. P. R., Montreal, P.Q.
GAGLIANO, DR. A., North Bay, Ont.
GARLAND, DR. J. M. B., Kingston, Ont.
GILES, DR. R. C., Winnipeg, Man.
GOODHALL, DR. P. O., Calgary, Alta.
HAGEN, DR. J. M., Edmonton, Alta.
HAMELIN, DR. L.-P., Trois-Rivieres, P.Q.
HAYAKAWA, DR. J., Winnipeg, Man.
HEBERT, DR. C. D., Quebec, P.Q.
HORNE, DR. G. M., Toronto, Ont.
HUGHES, DR. E. N., Victoria, B.C.
JOBIDON, DR. A., Quebec, P.Q.
JOHANNESSON, DR. T., Winnipeg, Man.
KEIL, DR. A. M., Calgary, Alta.
KRYT, DR. M., Toronto, Ont.
LAVOIE, DR. J. G. G., Montreal, P.Q.
LAYCRAFT, DR. G. H., Regina, Sask.
LUNDQUIST, DR. A. S. M., Peterborough, Ont.
MATHESON, DR. D. I., Toronto, Ont.
OTTON, DR. P. E., Montreal, P.Q.
PARANT, DR. F., Quebec, P.Q.
PARMENTER, DR. E. A., Toronto, Ont.
PATOINE, DR. J.-G., Quebec, P.Q.
PEISLEY, DR. H. N., St. John's, Nfld.
PETRASEK, DR. A., Montreal, P.Q.
PETROVICH, DR. E., Akron, Ohio, U.S.A.
POIRIER, DR. F. L., Quebec, P.Q.
READY, DR. N. H., Ottawa, Ont.
RENSAA, DR. M. A., Montreal, P.Q.
SCREECH, DR. G., Vancouver, B.C.
SKINNER, DR. L. C., Regina, Sask.
SLOAN, DR. I. A., Toronto, Ont.
SMITH, DR. J. A., Windsor, N.S.
TENCH, DR. J. F., Oakville, Ont.
WALKER, DR. D. A., San Francisco, California, U.S.A.
WILLIAMS, Dr. F. G., Vancouver, B.C.
YORK, DR. J. E., Toronto, Ont.

BOOK REVIEW

HYPOTHERMIA FOR THE NEUROSURGICAL PATIENT, By Antonio Boba, M.D. Springfield: Charles C. Thomas. Toronto: The Ryerson Press. 1960. $6.50.

In this short book the author has attempted to place before the anaesthetist sufficient data to carry out hypothermic anaesthesia for neurosurgical operations. It must be assumed that those who would make use of the book have reached a high standard of training in their specialty and also that they have had considerable experience in the management of poor risk patients. The book may also be of assistance to senior graduate students as an aid to practical teaching in a neurosurgical unit.

The physiology of hypothermia is reviewed at some length, and the bibliography is fairly extensive. More emphasis might be placed upon the fact that very little, if anything, is known of what is "normal" in an anaesthetized hypothermic patient. Until individual studies of organ and cellular metabolism and respiration can be carried out, there will be no means of establishing the "normal" state.

A discussion of typical cases is always beneficial. In this section a more complete discussion of the method and criteria of selection of cases is omitted. Examples of positive and relative contra-indications to this type of procedure and illustrations of the complications which might arise resulting from the abnormalities is of prime concern to anaesthetists, surgeons, and physicians, and should be included.

The summaries and conclusions at the end of each section provide a ready reference and quick review. It is hoped that graduate students will understand that this book is a summary of the bibliography, which must be read, and not presume that the book is an expansion of the conclusions which may be memorized for examination purposes.

B.M.

HYPOTHERMIA IN SURGICAL PRACTICE. By Keith Cooper and Donald Ross. Toronto: Cassell and Company Ltd. 1960. $3.35.

This book is a useful introduction to the subject of hypothermia and is suitable for the student of anaesthesia or surgery. It provides a general outline of hypothermia as seen in present-day surgical practice.

The initial chapters provide a sound background of basic physiology and pharmacology. The remaining chapters deal with most methods and types of cooling, including unintentional hypothermia! A long list of references provides additional sources of information. It is of value to those entering the field of hypothermia but is not suitable for those interested in its more detailed aspects.

A.W.C.

A DOCTOR'S MEMOIRS, By A. I. WILLINSKY. Toronto: The Macmillan Company of Canada Ltd. 1960. $4.25.

THIS IS the autobiography of a Jewish graduate of the University of Toronto in the year 1908. Though he ranked in the top twelve of his class, he was unable to secure an appointment as interne at any of the teaching hospitals of his own city. It was apparent at that date that the major teaching hospitals excluded those of his faith from those posts. In this connection it may be noted that at that time the proportion of Jewish students in the medical school was very small. Undismayed, though somewhat disillusioned, Dr. Willinsky after short periods of practice at Toronto and as *locum tenens* in the country went abroad to further his post-graduate training, a policy in which he persevered intermittently for a number of years. For a man of ability and aggressive by nature, study at Vienna, Dublin and major centres in the United States provided the experience from which he was able to institute certain projects not then well-established in Toronto. While not the first to give spinal anaesthetics in that city, he was the first to reinstitute this procedure, one which had fallen into disrepute there as in most parts of the medical world. Following his studies with Labat at Paris, he pioneered also in conduction anaesthesia. He appears to have been the first to institute prostatectomy by the transurethral route. Quite early in his career he became associated with the Toronto Western Hospital, eventually as surgeon in charge of the Department of Urology, a post he held with distinction until his retirement. By his industry and perseverance in the face of racial prejudices, he fashioned for himself a prominent place in medical circles of his native city.

Dr. Willinsky acknowledges that by being obliged to secure his post-graduate training abroad, his failure to obtain internship at Toronto proved to be a blessing. Any bitterness which he may have felt is perhaps reflected in the circumstance that in these memoirs he has few kind things to say of his Alma Mater and of those members of the profession prominent in his early days in the teaching hospitals of Toronto. It is natural that most of his encomiums were reserved chiefly for members of the staff of the Western Hospital, men with whom he was most closely associated.

Autobiography is not the easiest of literary endeavours and this one has a few minor defects. It is a rambling story digressing here and there in its themes. Nevertheless, the book provides interesting reading for both lay persons and the medical profession. In the final chapter, included as an appendix, the author provides his readers with recordings of recent conversations he had with his aged mother for whom he had great reverence. For this reviewer, this was one of the most interesting features of the book.

H.J.S.

BRITISH OXYGEN CANADA PRIZE

BRITISH OXYGEN CANADA LIMITED have made available the sum of $1,000 annually for a prize to be awarded by the Canadian Anaesthetists' Society for the best original work in Anaesthesia completed in Canada during the year preceding the award. The first such prize will be awarded at the time of the Annual Meeting of the Canadian Anaesthetists' Society in 1961. The following regulations apply:

Qualifications

(1) Applicant must be a resident in training in Anaesthesia or a practising anaesthetist.
(2) The study must be carried out in a Canadian Hospital or University, and must have been completed during the previous 12 months.
(3) The study submitted may be of a basic or clinical nature.

Submission and Selection

(1) Applicant's study is to be submitted in quadruplicate to the Secretary, Canadian Anaesthetists' Society, prior to April 1.
(2) Three (3) referees will be appointed by the Executive of the Canadian Anaesthetists' Society from departments of Anaesthesia in Canadian Universities. Not more than one referee shall be chosen from any one University.
(3) The prize-winning report or reports shall be presented at the Annual Meeting of the Canadian Anaesthetists' Society at which the award will be made, and will be subject to exclusive publication in the Canadian Anaesthetists' Society Journal. The right of publication of all reports submitted in application for the prize is reserved to the Canadian Anaesthetists' Society Journal subject to acceptance by the Editor.
(4) In the event of two (2) applicants submitting work judged by the referees to be of equal merit, the award may be divided at the discretion of the referees.
(5) If in the opinion of the referees the studies submitted do not warrant the award being made in any year, the prize will be deferred.

MEETINGS

CANADIAN ANAESTHETISTS' SOCIETY, ANNUAL GENERAL MEETING
Seigniory Club, Montebello, P.Q.

May 15–18, 1961

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, ANNUAL CONGRESS
Shamrock Hotel, Houston, Texas

April 9–13, 1961

BIENNIAL WESTERN CONFERENCE ON ANESTHESIOLOGY
Sheraton Hotel, Portland, Oregon

May 16–18, 1961

XI[E] CONGRÈS FRANÇAIS D'ANESTHÉSIOLOGIE
Nancy

May 18–21, 1961

ATLANTIC DIVISIONS, CANADIAN ANAESTHETISTS' SOCIETY
Brunswick Hotel, Moncton, N.B.

April 21–22, 1961

Guest speakers: Dr. Robert M. Smith, Children's Hospital, Boston
Dr. John R. Lincoln, Portland, Maine